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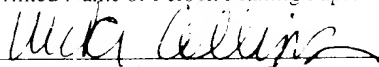
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NUCLEOTIDE ANALOGSBackground of the Invention

The present invention relates to novel nucleotide analog amidates and
 15 esters, their pharmaceutically acceptable acid addition salts, a process for their
 production, and to their use. The nucleotides of the present invention
 exhibit antitumor/antineoplastic activity, a broad spectrum of antimicrobial
 activity and certain other desirable activities.

Compounds related to the nucleotide analogs of the present invention
 20 may be found in: U.S. Patent Numbers 5,043,339, 5,108,994 and 5,166,198; EP
 206 459; EP 253 412; EP 269 947; EP 270 885; EP 319 228; EP 343 133; EP 398 231; EP
 404 296; EP 465 297; EP 468 119; EP 468 866; EP 479 640; EP 481 214; EP 494 370;
 EP 531 597; PCT/GB91/01171; PCT/US92/01020; PCT/US92/05208; WO
 91/19721; Bronson et al, Bioorg Medicinal Chem Lett (1992) 2:685-690;
 25 Bronson et al, J Med Chem (1989) 32:1457-1463; Bronson et al, Nucleotide
Analogs as Antiviral Agents, ACS Symposium Series 401, J.C. Martin, Ed., p.
 72-87, American Chemical Society, Washington, DC (1989); Colla, et al, J Med
Chem (1983) 26:602-604; Curley, et al, Antiviral Res (1990) 14:345-356; De
 Clercq, et al, Nature (1986) 323:464-467; Farrow, et al, J Med Chem (1990)
 30 33:1400-1406; Farquhar, et al, J. Pharm Sci (1983) 72:324-325; Freed, et al,
Biochem Pharmacol (1989) 19:3193-3198; Freeman, et al, J Med Chem (1992)
 35 35:3192-3196; Gabrielsen, B., et al, Antiviral Res Suppl I (1992) 17:149;
 Gumport, et al, Proc Natl Acad Sci (1971) 2559-2563; Juodka, et al, Coll Czech
Chem Commun (1974) 39:963-968; Kim, et al, Bioorg Medicinal Chem Lett
 (1992) 2:367-370; Kim, et al, Tet Lett (1992) 33:25-28; Kim, et al, J Med Chem
 (1990) 33:1207-1213; Kumar, et al, J Med Chem (1990) 33:2368-2375; McGuigan,
 et al, Antiviral Chem Chemother (1993) 4:97-101; McGuigan, et al, Antiviral
Res (1991) 15:255-263; Rosenberg, et al, Coll Czech Chem Commun (1988)
 53:2753-2777; Rosenberg, et al, Coll Czech Chem Commun (1988) 52:2792-2800;
 40 Rosenberg, et al, Coll Czech Chem Commun (1988) 52:2801-2808; Starrett, et

al, Antiviral Res (1992) 19:267-273; Yu, et al, J Med Chem (1992) 35:2958-2969; Wolff-Kugel, et al, Tet Lett (1991) 32:6341-6344.

A characteristic of nucleotide analogs or nucleotides having a phosphonate or a phosphate group is the presence of one or two negative charges associated with the phosphorus group at physiologic pH. The charge associated with moieties such as phosphate or phosphonate groups is believed to generally limit bioavailability by limiting cell membrane permeation via passive diffusion (Liebman, et al, J Biol Chem, (1955) 216:823-830; Roll, et al, J Biol Chem, (1956) 220:439-444; Srivastava, et al, Bioorg Chem (1984) 12:118-129; Palu, et al, Antiviral Res (1991) 16:115-119; Sastry, et al, Mol Pharmacol (1992) 41:441-445). These compounds are often, therefore, given parenterally in order to enhance bioavailability by increasing serum or intracellular levels.

Other characteristics of nucleotide analogs that can limit their efficacy include unfavorable pharmacokinetic or pharmacodynamic properties, insufficient potency and/or unfavorable toxicity characteristics.

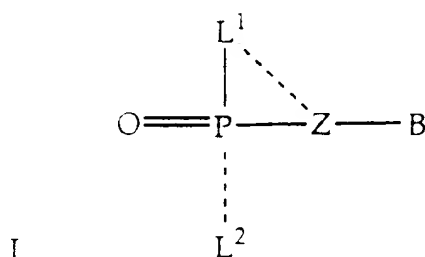
Studies were conducted to ameliorate one or more of the above-mentioned problems associated with nucleotide analog drugs. The present invention includes novel nucleotide analogs that are hydrolyzable in vivo. The nucleotide analogs can have improved bioavailability, improved pharmacokinetic or pharmacodynamic properties, enhanced potency and/or improved toxicity characteristics compared to the corresponding unmodified nucleotide analog. Methods to synthesize and use the compounds and methods to obtain and use antibodies that recognize the compounds are also disclosed.

Summary of the Invention

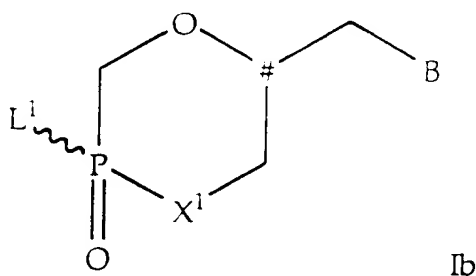
In a principal embodiment, the objects of this invention are accomplished by a nucleotide analog amidate comprising a phosphonate radical wherein the improvement comprises an amino acid residue or polypeptide radical in which an amino group of the amino acid or polypeptide is bonded to the phosphorus atom of the nucleotide analog by an amidate bond, a carboxyl group of the amino acid residue or polypeptide radical is positioned such that it is capable as the free acid of hydrolyzing the phosphoroamidate bond, and the carboxyl group is blocked (such as by

moieties including esters or amides). The nucleotide analog amidates of this invention are hydrolyzed in vivo to the corresponding nucleotide analog and are thus precursors of the corresponding nucleotide analog.

In accordance with this invention the nucleotide analog amidates or a physiologically acceptable salt thereof, have the structure of formula I



wherein L^1 and L^2 are independently an amino acid or polypeptide residue bonded to the phosphorus atom of the nucleotide analog by an amidate bond, or L^1 or L^2 are an oxyester, thioester, a substituted or unsubstituted amine, or hydroxy, provided that one or both of L^1 and L^2 is an amino acid or polypeptide residue and any carboxyl group that is linked by less than about 5 atoms to the amidate N is esterified or amidated, the dotted lines represent facultative bonds and wherein, (i) P and Z are linked to form a compound of the formula Ib



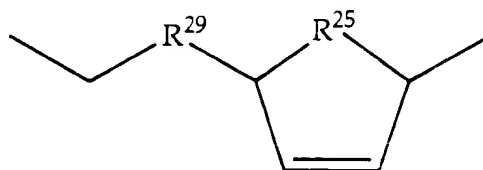
or (ii) L^1 and Z are linked to form a compound of the formula Ic



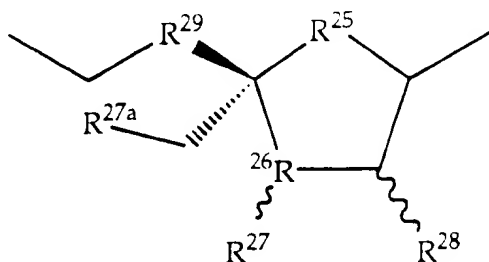
substituents linked to carbon atoms designated # are in the *R*, *S* or *RS* configuration;

$$Z \text{ is } -\text{CHR}^7-\text{R}^{11}-(\text{CH}_2)_{m1}-\text{C}^\#(\text{R}^8)((\text{CH}_2)_{m2}(\text{R}^9))-(\text{CH}_2)_{m3}-\text{R}^{10}-(\text{CH}_2)_{m4}-,$$

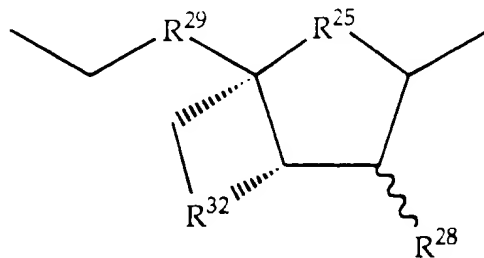
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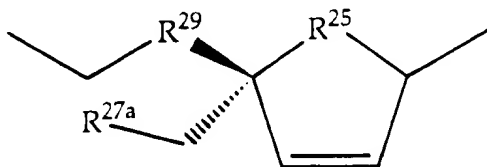
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VII



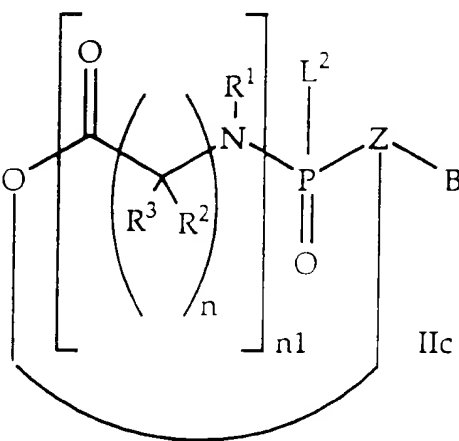
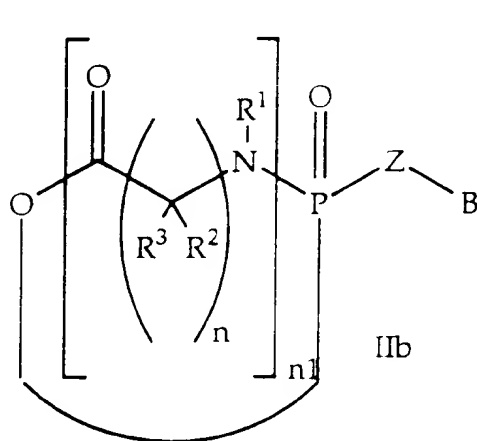
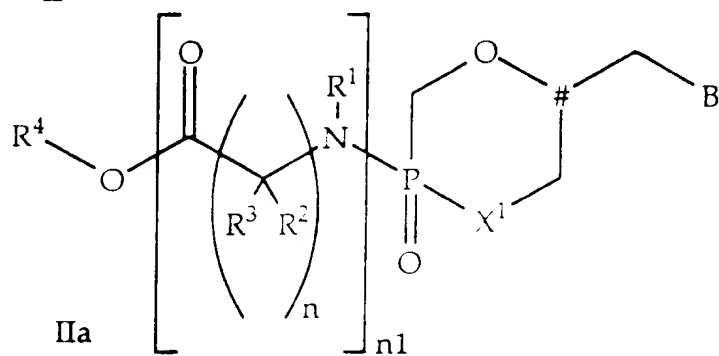
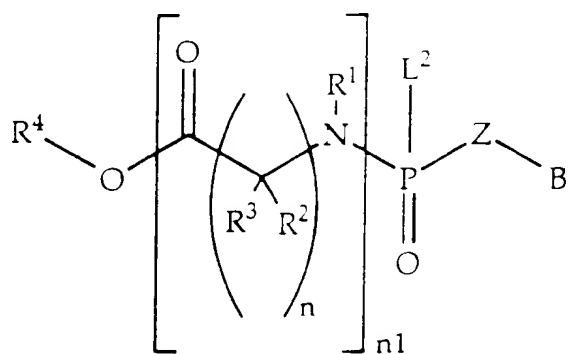
or

VIII

wherein

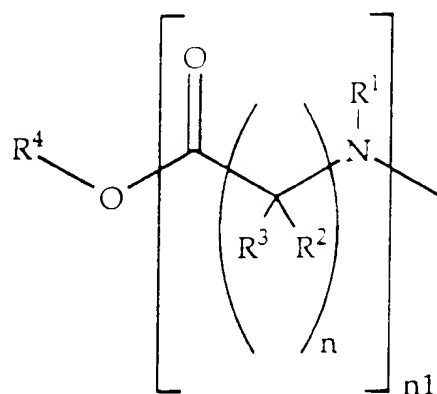
- 5 R^7 is H or C_1 - C_4 alkyl;
 R^8 is H or C_1 - C_4 alkyl, C_2 - C_4 alkenyl, azidomethyl or azidoethyl;
 R^9 is halogen (F, Cl, Br or I), H or OH;
 R^{10} is O, CH_2 or a chemical bond;
 R^{11} is O, S, CH_2 , CHF or CF_2 ;
 Q is $-C(R^{12})_2-CH_2-$, $-C(R^{12})_2-O-$, $-CR^{12}=CR^{12}-$, or $-C\equiv C-$, wherein each R^{12}
10 is independently H, or halogen;
 R^{13} is H, halogen, OH, CH_3 , CH_2OH , or $C_3 - C_6$ acyloxymethyl;
 R^{14} is H, halogen, OH, CH_3 , CH_2OH , $C_3 - C_6$ acyloxymethyl, or $C_2 - C_6$
acyloxy;
 R^{25} is CH_2 , CHF or O;
15 R^{26} is CH or S, provided that when R^{25} is CH, R^{26} is not S;
 R^{27} is H, OH, halogen, N_3 , C_1 - C_4 alkyl, C_1 - C_4 alkoxy or, when R^{26} is S,
 R^{27} is absent;
 R^{27a} is H, OH, halogen, N_3 , C_1 - C_4 alkyl, C_1 - C_4 alkoxy;
 R^{28} is H, OH, halogen, N_3 , C_1 - C_4 alkyl or C_1 - C_4 alkoxy;
20 R^{29} is O, S, CH_2 , CHF, CF_2 ;
 R^{32} is O;
 m1 is an integer having a value from 0 to 4;
 m2 is an integer having a value from 0 to 4;
 m3 is an integer having a value from 0 to 4;
25 m4 is an integer having a value from 0 to 4;
 B is a heterocyclic base; and
 substituents linked to the carbon atom designated $C^\#$ are in the *R*, *S* or
RS configuration.

- 30 In a further embodiment the objects are accomplished by compounds
of the formula II, IIa, IIb and IIc



5

wherein L^2 is OR, SR or



III

n is an integer having a value from 1 to 5 and if $n > 1$, each $-C(R^3)(R^2)-$ may be the same or different;

5 $n1$ is an integer;

substituents linked to the carbon atom designated # are in the R , S or RS configuration;

R is H , C_1 - C_{20} alkyl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH , O , N and halogen (F , Cl , Br , I), C_3 - C_{20} aryl which is unsubstituted or substituted by substituents independently selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl (1 to 3 halogen atoms), cyano, nitro, OH , O , N and halogen or R is C_4 - C_{20} aryl-alkyl which is unsubstituted or substituted in the aryl moiety by substituents independently selected from the group
15 consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl (1 to 3 halogen atoms), cyano, nitro, OH , O , N and halogen, or R is C_3 - C_{24} 1-acyloxy-1-alkyl (C_1 - C_8 alkyl), or R is C_6 - C_{24} 1-acyloxy-1-aryl-1-alkyl (C_1 - C_6 aryl, C_1 - C_4 alkyl), or R is C_3 - C_{24} 1-acyloxy-2-alkoxy-1-alkyl (C_1 - C_8 alkyl), or R is C_3 - C_{24} 1-acyloxy-2-haloalkyl (C_1 - C_8 haloalkyl, 1 to 3 halogen atoms);

20 R^1 is H or C_1 - C_9 alkyl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH , O , N , $COOR^4$ and halogen, C_3 - C_6 aryl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH , O , N , $COOR^4$ and halogen or C_3 - C_9 aryl-alkyl which is unsubstituted or substituted
25 by substituents independently selected from the group consisting of OH , O , N , $COOR^4$ and halogen;

R² is H or C₁-C₉ alkyl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N, COOR⁴ and halogen, C₃-C₆ aryl which is unsubstituted or substituted by
5 substituents independently selected from the group consisting of OH, O, N, COOR⁴ and halogen or C₃-C₉ aryl-alkyl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N, COOR⁴ and halogen;

R³ is C(O)-OR⁴, amino, amide, guanidiny, imidazolyl, indolyl,
10 sulfoxide, phosphoryl, C₁ - C₃ alkylamino, C₁ - C₃ alkylidamino, C₁ - C₆ alkenylamino, hydroxy, thiol, C₁ - C₃ alkoxy, C₁ - C₃ alkthiol, (CH₂)_nCOOR⁴, C₁-C₆ alkyl which is unsubstituted or substituted with OH, halogen, SH, NH₂, phenyl, hydroxyphenyl or C₇ - C₁₀ alkoxyphenyl; C₂-C₆ alkenyl which is unsubstituted or substituted with OH, halogen, SH, NH₂, phenyl,
15 hydroxyphenyl or C₇ - C₁₀ alkoxyphenyl; C₆-C₁₂ aryl which is unsubstituted or substituted with OH, halogen, SH, NH₂, phenyl, hydroxyphenyl or C₇ - C₁₀ alkoxyphenyl; and

R⁴ is H provided that n₁ greater than 1, or is C₃-C₉ alkyl which is substituted by substituents independently selected from the group consisting
20 of OH, O, N and halogen, C₃-C₆ aryl which is substituted by substituents independently selected from the group consisting of OH, O, N and halogen or C₃-C₉ aryl-alkyl which is substituted by substituents independently selected from the group consisting of OH, O, N and halogen.

The structural formula I is meant to define compounds where the
25 phosphorus (P) atom is tetravalent (PV oxidation state) and optionally linked via the facultative bonds shown as dotted lines to either L¹ or Z to form a heterocyclic ring containing at least the P atom itself and a nitrogen atom of L¹ or an atom present, usually oxygen (O), in Z. For such compounds, L₂ and the facultative bond between P and Z is absent. Such heterocyclic rings will
30 preferably be 5-, 6- or 7-membered, but are also 4-, 8-, 9-, 10-, 11- or 12-membered. Alternatively the P atom is covalently linked to L² with L¹ and Z optionally linked to each other to form a heterocyclic ring. The structure is not intended to include compounds where L¹, L² and a heterocyclic ring containing P and Z are present in the same molecule which would exceed the
35 valency of P. Thus, an exemplary class of compounds is represented by the

structure of formula I includes $(L^1)(L^2)P(O)-Z-B$ (formula Id) where no heterocyclic rings are formed between any L^1 , L^2 , P, Z or B moiety.

R^2 includes methyl, ethyl, propyl, isopropyl and benzyl.

In another embodiment, the objects of this invention are accomplished
5 by a nucleotide analog ester comprising a phosphonate radical and an ester moiety bonded to the phosphorus atom of the nucleotide analog. The nucleotide analog esters of this invention are hydrolyzed in vivo to the corresponding nucleotide analog and are thus precursors of the corresponding nucleotide analog, or can be used as intermediates in the
10 synthesis of the nucleotide analog amidates.

The substructure Z can have a range of atoms between the base, B, and the phosphorus atom. For example, four atoms separate the heterocyclic base and phosphorus moieties when Z is of the formula $-CH_2-O-CH_2-CH_2-$. In general, there will be from 2 to 16 atoms, preferably from 3 to 9 atoms, more
15 preferably from 4 to 6 atoms that separate the heterocyclic base and the phosphorus atom. Thus, Z substructures of the formula $-CHR^7-R^{11}-(CH_2)_{m1}-C(R^8)((CH_2)_{m2}(R^9))-(CH_2)_{m3}-R^{10}-(CH_2)_{m4}-$ may be characterized where the sum of $m1$, $m3$ and $m4$ is in a range between 0 and 12 or preferably in a range between 1 and 6, more preferably in a range between 1 and 4.

20 The nucleotide analog amidate and ester compounds of the instant invention include the corresponding salts, which may be base salts of the phosphonic acid moiety or an acid addition salt of the base in addition to the zwitterionic forms and/or solvates of compounds of formula I.

Some of the compounds of the present invention can exist as optical
25 isomers and both racemic or scalemic and diastereomeric mixtures of these isomers which may exist for certain compounds as well as the individual optical isomers which are all within the scope of the present invention. Compounds of formula IIa in the *R*, *S* or *RS* configuration at the chiral carbon, designated # herein, are examples of compounds having optical
30 isomers. While the scalemic mixtures can be separated into their individual isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, e.g. acids or bases followed by conversion back to the optically active substrates; in most instances, for compounds of the present invention, the preferred optical

isomer can be synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

As indicated, the present invention also pertains to the salts, including pharmaceutically acceptable non-toxic salts of these compounds. Such salts
5 may include those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or ammonium and quaternary amino ions with the acid anion moiety of the phosphonic acid group. In addition salts may be formed from acid addition of certain organic and inorganic acids with basic centers of the purine, specifically guanine, or pyrimidine base.
10 Finally it is to be understood that compounds of the present invention in their un-ionized as well as zwitterionic form and/or in the form of solvates are also considered part of the present invention.

In other embodiments, the foregoing nucleotide analog amidates and esters or their dihydroxy phosphonate hydrolysis products are labeled with a
15 detectable tag such as a radioisotope (including ^{32}P , ^{35}S , ^{14}C , ^3H , ^{125}I), a fluorescent moiety, an enzyme (including peroxidase, phosphatase) or the like.

In other embodiments, the foregoing nucleotide analog amidates comprise amino acid, dipeptide or tripeptide compounds (monosubstituted or
20 disubstituted with identical or different amino acid, dipeptide or tripeptide substituents) that are capable of entry into eukaryotic cells via amino acid or peptide transporters present in eukaryotic cells *in vivo* or *in vitro*.

Also included are immunogens for raising antibodies which are capable of binding to the nucleotide analog amidates and esters of this
25 invention and/or their dihydroxy phosphonate hydrolysis products, as well as antibodies capable of binding to the amidate and ester compounds of this invention or to their dihydroxy phosphonate hydrolysis products.

Chemical Structures

30 Structural formulas and substructures are represented as roman numerals (I, II, III, IV, V, etc) or as letters (B, Z, L^1 , L^2 , R^1 , R^2 , etc). The substructures Z and Z^1 represent linking groups between the heterocyclic base (B) and the phosphorus atom (P) of the phosphonate group in the nucleotide analogs described herein. Linking groups Z, such as $-\text{CHR}^7-\text{R}^{11}-(\text{CH}_2)_{\text{m}1}-$
35 $\text{C}(\text{R}^8)((\text{CH}_2)_{\text{m}2}(\text{R}^9))-(\text{CH}_2)_{\text{m}3}-\text{R}^{10}-(\text{CH}_2)_{\text{m}4}-$, in the structure $(\text{L}^1)(\text{L}^2)\text{P}(\text{O})-\text{Z}-\text{B}$

have the structure $(L^1)(L^2)P(O)-CHR^7-R^{11}-(CH_2)_{m1}-C(R^8)((CH_2)_{m2}(R^9))-(CH_2)_{m3}-R^{10}-(CH_2)_{m4}-B$ (i.e. the heterocyclic base (B) is covalently linked to the unfilled valence on the right side of the structure and the phosphorus atom is linked to the unfilled valence on the left side).

5

Brief Description of the Drawings

Figure 1. Synthesis of formula Ib compounds where X^1 is S.

Figure 2. Synthesis of formula Ia compounds.

Figure 3. Synthesis of formula IV compounds.

10 Figure 4. Synthesis of formula VII compounds.

Figure 5. Synthesis of formula VIII compounds.

Figure 6. Synthesis of formula VI compounds.

Figure 7. Synthesis of formula VI compounds.

15 Detailed Description of the Invention

Amino Acid Residues. When groups L^1 or L^2 comprise an amino acid residue they comprise any naturally-occurring or synthetic amino acid residue, i.e., any moiety comprising at least one carboxyl and at least one amino residue directly linked by at least one carbon atom, typically a single (α) carbon atom. The nature and identity of the intervening structure located between the carboxyl and amino (amidate) groups can have a variety of structures including those described herein. All that is necessary is that the group have sufficient conformation and length to be capable of acid catalysis of the phosphoroamidate bond and release of the phosphonate when the free carboxyl is generated in vivo, e.g. by deesterification, deamidation or peptidolytic cleavage of the precursor. In general, the amino acids corresponding to the residues employed in the compounds of this invention are naturally occurring and have no pharmacological activity *per se*. However, optimal pharmacokinetic activity (substantially complete autocatalytic hydrolysis upon hydrolysis of the distal amide or ester bond) may be achieved by using non-naturally occurring amino acid residues. The intervening structure may be as simple as methylene (when the residue is glycyl) or substituted methylene (other α amino acids). The structure ordinarily contains up to about 5 carbon or hetero atoms in the direct linkage between the carboxyl carbon and the amidate nitrogen, as for example in the

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case of intervening ethylene, propylene, butylene, or pentylene groups or their substituted analogs, such as for example oxyesters in which O replaces carbon and, as appropriate, hydrogen. An example of such an intervening
5 structure would be $-\text{CH}-\text{O}-\text{CH}(\text{R}^3)(\text{R}^2)-$. In general, fewer intervening atoms are employed when more rapid hydrolysis is desired, although it will be understood that larger structures are suitable if they possess sufficient flexibility or have conformations in which the carboxyl group is positioned in proximity to the amidate bond.

10 In general, the amino acid residue has the structure shown in formula III. Ordinarily, n is 1 or 2, R^2 is H and R^3 is a moiety containing one or more of the following groups: amino, carboxyl, amide, carboxyl ester, hydroxyl, C_6 - C_7 aryl, ether, n -, s - or t -alkyl ($\text{C}_1 - \text{C}_6$), guanidinyl, imidazolyl, indolyl, sulfhydryl, sulfoxide, and phosphoryl. The R^2 and R^3 substituents can have a
15 wide variety of structures including those disclosed herein.

Ordinarily R^2 is H and R^3 is a side chain or group of a naturally occurring amino acid. With respect to the carboxyl-containing side chains it will be understood that if the C atom of the subject carboxyl is linked by 5 or less atoms to the phosphoamide N then the carboxyl optionally will be
20 blocked, e.g. by esterification or amidation wherein the ester or amide bonds are hydrolyzable in vivo. R^3 also is taken together with R^1 to form a proline residue ($\text{R}^3 = -\text{CH}_2-$)₃). Thus, R^3 is generally a side group such as H, $-\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2-\text{CH}(\text{CH}_3)_2$, $-\text{CHCH}_3-\text{CH}_2-\text{CH}_3$, $-\text{CH}_2-\text{C}_6\text{H}_5$, $-\text{CH}_2\text{CH}_2-\text{S}-\text{CH}_3$, $-\text{CH}_2\text{OH}$, $-\text{CH}(\text{OH})-\text{CH}_3$, $-\text{CH}_2-\text{SH}$, $-\text{CH}_2-\text{C}_6\text{H}_4\text{OH}$, $-\text{CH}_2-\text{CO}-\text{NH}_2$, $-\text{CH}_2-\text{CH}_2-$
25 $\text{CO}-\text{NH}_2$, $-\text{CH}_2-\text{COOH}$, $-\text{CH}_2-\text{CH}_2-\text{COOH}$, $-(\text{CH}_2)_4-\text{NH}_2$ and $-(\text{CH}_2)_3-\text{NH}-\text{C}(\text{NH}_2)-\text{NH}_2$. R^3 also includes 1-guanidinoprop-3-yl, benzyl, 4-hydroxybenzyl, imidazol-4-yl, indol-3-yl, methoxyphenyl and ethoxyphenyl. The optimal R^3 group is readily selected using routine assays.

When the amino acid residues contain one or more chiral centers, any
30 of the D, L, meso, threo or erythro (as appropriate) racemates, scalemates or mixtures thereof, fall within the scope of this invention. In general, if it is desired to rely on non-enzymatic means of hydrolysis, D isomers should be used. On the other hand, L isomers may be more versatile since they can be susceptible to both non-enzymatic as well as potential targeted enzymatic
35 hydrolysis, and are more efficiently transported by amino acid or dipeptidyl transport systems in the gastrointestinal tract.

Examples of suitable amino acid residues include the following:

Glycyl;

Aminopolycarboxylic acids, e.g., aspartic acid, β -hydroxyaspartic acid, glutamic acid, β -hydroxyglutamic acid, β -methylaspartic acid, β -methylglutamic acid, β,β -dimethylaspartic acid, γ -hydroxyglutamic acid, β,γ -dihydroxyglutamic acid, β -phenylglutamic acid, γ -methyleneglutamic acid, 3-aminoadipic acid, 2-aminopimelic acid, 2-aminosuberic acid and 2-aminosebacic acid residues;

Amino acid amides such as glutaminy and asparaginy;

Polyamino- or polybasic-monocarboxylic acids such as arginine, lysine, β -aminoalanine, γ -aminobutyric acid, ornithine, citrulline, homoarginine, homocitrulline, 5-hydroxy-2,6-diaminohexanoic acid (commonly, hydroxylysine, including allohydroxylysine) and diaminobutyric acid residues;

Other basic amino acid residues such as histidiny;

Diaminodicarboxylic acids such as α,α' -diaminosuccinic acid, α,α' -diaminoglutaric acid, α,α' -diaminoadipic acid, α,α' -diaminopimelic acid, α,α' -diamino- β -hydroxypimelic acid, α,α' -diaminosuberic acid, α,α' -diaminoazelaic acid, and α,α' -diaminosebacic acid residues;

Imino acids such as proline, 4- or 3-hydroxy-2-pyrrolidinecarboxylic acid (commonly, hydroxyproline, including allohydroxyproline), γ -methylproline, piperidine-2-carboxylic acid, 5-hydroxypiperidine-2-carboxylic acid, $-N([CH_2]_nCOOR^4)_2$, wherein n and R^4 are as defined above, and azetidine-2-carboxylic acid residues;

A mono- or di-alkyl (typically $C_1 - C_8$ branched or normal) amino acid such as alanine, valine, leucine, allylglycine, butyric acid, norvaline, norleucine, heptyline, α -methylserine, α -amino- α -methyl- γ -hydroxyvaleric acid, α -amino- α -methyl- δ -hydroxyvaleric acid, α -amino- α -methyl- ϵ -hydroxycaproic acid, isovaline, α -methylglutamic acid, α -aminoisobutyric acid, α -aminodiethylacetic acid, α -aminodiisopropylacetic acid, α -aminodi- n -propylacetic acid, α -aminodiisobutylacetic acid, α -aminodi- n -butylacetic acid, α -aminoethylisopropylacetic acid, α -amino- n -propylacetic acid, α -aminodiisobutyric acid, α -methylaspartic acid, α -methylglutamic acid, 1-aminocyclopropane-1-carboxylic acid; isoleucine, alloisoleucine, tert-leucine,

β -methyltryptophan and α -amino- β -ethyl- β -phenylpropionic acid residues; β -phenylserinyl;

Aliphatic α -amino- β -hydroxy acids such as serine, β -hydroxyleucine, β -hydroxynorleucine, β -hydroxynorvaline, and α -amino- β -hydroxystearic acid
5 residues;

α -Amino, α -, γ -, δ - or ϵ -hydroxy acids such as homoserine, γ -hydroxynorvaline, δ -hydroxynorvaline and epsilon-hydroxynorleucine residues; canavinyl and canalinyl; γ -hydroxyornithinyl;

2-hexosaminic acids such as D-glucosaminic acid or D-galactosaminic
10 acid residues;

α -Amino- β -thiols such as penicillamine, β -thiolnorvaline or β -thiolbutyrine residues;

Other sulfur containing amino acid residues including cysteine; homocystine; β -phenylmethionine; methionine; S-allyl-L-cysteine sulfoxide;
15 2-thiolhistidine; cystathionine; and thiol ethers of cysteine or homocysteine;

Phenylalanine, tryptophan and ring-substituted α amino acids such as the phenyl- or cyclohexylamino acids α -aminophenylacetic acid, α -aminocyclohexylacetic acid and α -amino- β -cyclohexylpropionic acid; phenylalanine analogues and derivatives comprising aryl, lower alkyl,
20 hydroxy, guanidino, oxyalkylether, nitro, sulfur or halo-substituted phenyl (e.g., tyrosine, methyltyrosine and o-chloro-, p-chloro-, 3,4-dichloro, o-, m- or p-methyl-, 2,4,6-trimethyl-, 2-ethoxy-5-nitro, 2-hydroxy-5-nitro and p-nitro-phenylalanine); furyl-, thienyl-, pyridyl-, pyrimidinyl-, purine or naphthylalanines; and tryptophan analogues and derivatives including
25 kynurenine, 3-hydroxykynurenine, 2-hydroxytryptophan and 4-carboxytryptophan residues;

α -Amino substituted amino acid residues including sarcosine (N-methylglycine), N-benzylglycine, N-methylalanine, N-benzylalanine, N-methylphenylalanine, N-benzylphenylalanine, N-methylvaline and N-benzylvaline; and
30

α -Hydroxy and substituted α -hydroxy amino acid residues including serine, threonine, allothreonine, phosphoserine and phosphothreonine residues.

Any one of the foregoing or other known amino acids are suitably
35 employed in this invention provided that they are capable of autocatalytically

hydrolyzing the amidate bond. Thus, they must contain, or must, upon being converted (hydrolyzed) in vivo, contain a free carboxyl group. In general, the amino acids corresponding to the residues employed in the compounds of this invention are naturally occurring and have no pharmacological activity.

5 However, optimal pharmacokinetic activity may be achieved by the use of non-naturally occurring amino acid residues.

Of particular interest are hydrophobic residues such as mono- or di-alkyl or aryl amino acids, cycloalkylamino acids and the like. These residues, together with R⁴, contribute to cell permeability by increasing the partition
10 coefficient of the nucleotide analog amidate. Typically, the residue does not contain a sulfhydryl or guanidino substituent.

Polypeptide Radicals. If n₁ is greater than 1, then the group shown in formula II, IIa, IIb or III is greater than 1, then the moiety comprises a
15 polypeptide radical. This comprises dipeptides, short polypeptides of 3, 5 or 10 residues, or proteins having up to 100 or more residues. For the most part, dipeptides not containing aspartic or glutamic acid in the residue adjacent to the P atom, will not autocatalytically hydrolyze the amidate bond and therefore the carboxyl groups (generally 1 or 2) in the distal residue do not
20 need to be esterified or amidated, i.e., R⁴ can be H in these circumstances. However, if such compounds are intended to be used as precursors for the free phosphonate nucleotide analog in vivo, rather than as immunogens for example, the polypeptides ordinarily will contain a peptidolytic enzyme cleavage site at the peptide bond linking the first residue and the next residue
25 distal to the phosphorus atom. Such cleavage sites are flanked by enzymatic recognition structures, e.g. particular residues recognized by a hydrolytic enzyme.

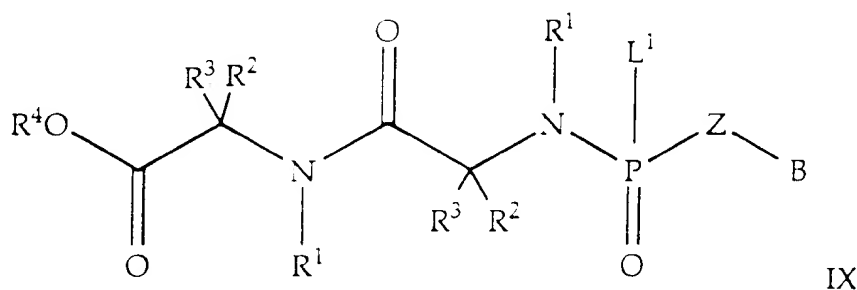
Peptidolytic enzymes are well known, and in particular include carboxypeptidases. Carboxypeptidases digest polypeptides by removing C-
30 terminal residues, and are specific in many instances for particular C-terminal sequences. Such enzymes and their substrate requirements in general are well known. For example, a dipeptide having a given pair of residues and a free carboxyl terminus is covalently bonded through its α -amino group to the phosphorus atom of the invention nucleotide analogs. It is expected that this
35 peptide will be cleaved by the appropriate dipeptidase or protease, leaving the

carboxyl of the proximal amino acid residue to autocatalytically cleave the amide bond.

Examples of suitable dipeptidyl groups (designated by their single letter code) include AA, AR, AN, AD, AC, AE, AQ, AG, AH, AI, AL, AK, AM, AF,
5 AP, AS, AT, AW, AY, AV, RA, RR, RN, RD, RC, RE, RQ, RG, RH, RI, RL, RK, RM, RF, RP, RS, RT, RW, RY, RV, NA, NR, NN, ND, NC, NE, NQ, NG, NH, NI, NL, NK, NM, NF, NP, NS, NT, NW, NY, NV, DA, DR, DN, DD, DC, DE, DQ, DG, DH, DI, DL, DK, DM, DF, DP, DS, DT, DW, DY, DV, CA, CR, CN, CD, CC, CE, CQ, CG, CH, CI, CL, CK, CM, CF, CP, CS, CT, CW, CY, CV, EA, ER, EN,
10 ED, EC, EE, EQ, EG, EH, EI, EL, EK, EM, EF, EP, ES, ET, EW, EY, EV, QA, QR, QN, QD, QC, QE, QQ, QG, QH, QI, QL, QK, QM, QF, QP, QS, QT, QW, QY, QV, GA, GR, GN, GD, GC, GE, GQ, GG, GH, GI, GL, GK, GM, GF, GP, GS, GT, GW, GY, GV, HA, HR, HN, HD, HC, HE, HQ, HG, HH, HI, HL, HK, HM, HF, HP, HS, HT, HW, HY, HV, IA, IR, IN, ID, IC, IE, IQ, IG, IH, II, IL, IK, IM, IF, IP, IS,
15 IT, IW, IY, IV, LA, LR, LN, LD, LC, LE, LQ, LG, LH, LI, LL, LK, LM, LF, LP, LS, LT, LW, LY, LV, KA, KR, KN, KD, KC, KE, KQ, KG, KH, KI, KL, KK, KM, KF, KP, KS, KT, KW, KY, KV, MA, MR, MN, MD, MC, ME, MQ, MG, MH, MI, ML, MK, MM, MF, MP, MS, MT, MW, MY, MV, FA, FR, FN, FD, FC, FE, FQ, FG, FH, FI, FL, FK, FM, FF, FP, FS, FT, FW, FY, FV, PA, PR, PN, PD, PC, PE, PQ, PG,
20 PH, PI, PL, PK, PM, PF, PP, PS, PT, PW, PY, PV, SA, SR, SN, SD, SC, SE, SQ, SG, SH, SI, SL, SK, SM, SF, SP, SS, ST, SW, SY, SV, TA, TR, TN, TD, TC, TE, TQ, TG, TH, TI, TL, TK, TM, TF, TP, TS, TT, TW, TY, TV, WA, WR, WN, WD, WC, WE, WQ, WG, WH, WI, WL, WK, WM, WF, WP, WS, WT, WW, WY, WV, YA, YR, YN, YD, YC, YE, YQ, YG, YH, YI, YL, YK, YM, YF, YP, YS, YT,
25 YW, YY, YV, VA, VR, VN, VD, VC, VE, VQ, VG, VH, VI, VL, VK, VM, VF, VP, VS, VT, VW, VY and VV.

Exemplary dipeptidyl compounds have the structure of formula IX wherein R^2 is H, R^3 is the side chain of a naturally occurring amino acid, L^1 , R^4 , B and Z are as defined above.

30



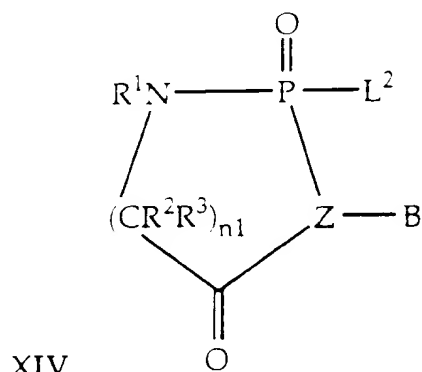
Tripeptides are also useful. The sequence -X4-pro-X5- (where X4 is any amino acid residue and X5 is an amino acid residue, a carboxyl ester of proline or hydrogen) will be cleaved by luminal carboxypeptidase to yield X4 with a free carboxyl, which in turn autocatalytically cleaves the phosphono amide bond. X5 usually will be a benzyl ester of the carboxy group of X5. Thus, n1 is usually 1, 2 or 3, but may range up to 5, 10, 100 or more residues.

If the amino acid residue has 2 or more amine groups, e.g., a lysinyl or arginyl, or ornithinyl residue, then R³ represents the group -[C(R⁶)₂]_{n2}N(R²)- where n2 is 0 to 6, R⁶ is H, C₁-C₂₀ alkyl, C₆-C₂₀ aryl, C₇-C₂₀ alkylaryl, C₇-C₂₀ arylalkyl, C₁-C₂₀ alkoxy, C₆-C₂₀ aryloxy or hydroxyl, and R² is defined above. Such compounds will contain a plurality of phosphonate moieties. For example when both the epsilon (ε)/delta (δ) and alpha (α) amino groups of lysine or ornithine are substituted with nucleotide phosphonate moieties the amide is believed to be capable of releasing two molecules of active drug, each expected to emerge under different pharmacokinetics and therefore further sustaining the drug release.

The number of amino acid residues, n1, in the nucleotide analog amides of this invention can vary extensively. Where n1=1, a single amino acid is found at the designated site, and where n1>1 then a polypeptide radical is present. Typically, n1 is 1 or 2, but may range up to 3, 5, 10 or 100 or more residues.

If the residue is immediately adjacent to the phosphonate atom and its side chain contains a carboxyl group, e.g. in the case of glutamic acid or aspartic acid, then this carboxylate is substituted with R⁴.

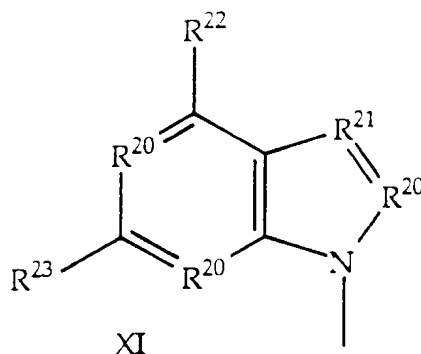
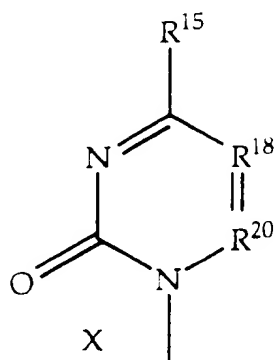
The amide group optionally is taken together with Z to form a cyclic amide precursor. Such compounds have structure XIV.

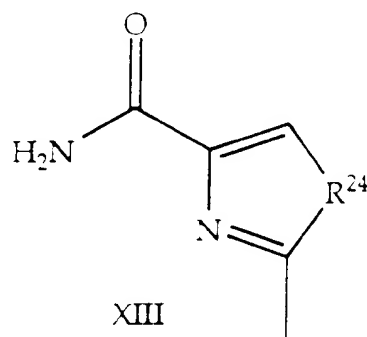
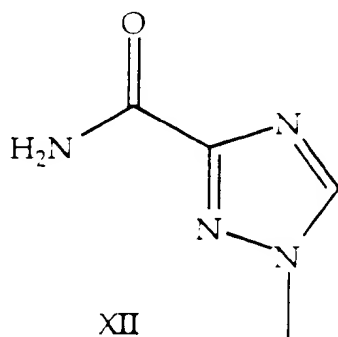


wherein L², R¹, R², R³, Z, n₁ and B are as defined above. Typically, in this embodiment R³ is not carboxyl, R² is H, and n₁ is 1.

Hydrolysis of the cyclic amidates of formulas IIa-c and IV leaves a hydroxyl-substituted substructure Z and the free carboxyl, which in turn will autolyze the amidate. Substructures Z in which the methylene backbone is substituted with hydroxymethyl are advantageous in this embodiment, particularly linkers in compounds of the formula -CH₂OCH(CH₂O-)CH₂-B.

Heterocyclic bases. The compounds of this invention comprise any naturally-occurring heterocycle found in nucleic acids, nucleotides or nucleosides, or analogs thereof. The radicals of such heterocyclic bases, designated herein as B, are generally the purine, pyrimidine or related heterocycles shown in formulas X-XIII.





wherein R^{15} is H, OH, F, Cl, Br, I, OR^{16} , SH, SR^{16} , NH_2 , or NHR^{17} ;

R^{16} is $C_1 - C_6$ alkyl including CH_3 , CH_2CH_3 , CH_2CCH (2-propynyl), CH_2CHCH_2 (2-allyl), C_3H_7 ;

R^{17} is $C_1 - C_6$ alkyl including CH_3 , CH_2CH_3 , CH_2CCH , CH_2CHCH_2 , C_3H_7 ;

R^{18} is N, CF, CCl, CBr, Cl, CR^{19} or CSR^{19} , COR^{19} ;

R^{19} is H, $C_1 - C_9$ alkyl, $C_2 - C_9$ alkenyl, $C_2 - C_9$ alkynyl or $C_7 - C_9$ aryl-alkyl unsubstituted or substituted by OH, O, N, F, Cl, Br or I including CH_3 , CH_2CH_3 , $CHCH_2$, $CHCHBr$, CH_2CH_2Cl , CH_2CH_2F , CH_2CCH , CH_2CHCH_2 , C_3H_7 , CH_2OH , CH_2OCH_3 , $CH_2OC_2H_5$, CH_2OCCH , $CH_2OCH_2CHCH_2$, $CH_2C_3H_7$, CH_2CH_2OH , $CH_2CH_2OCH_3$, $CH_2CH_2OC_2H_5$, CH_2CH_2OCCH , $CH_2CH_2OCH_2CHCH_2$, $CH_2CH_2OC_3H_7$;

R^{20} is N or CH;

R^{21} is N, CH, CCN, CCF_3 , $CC\equiv CH$ or $CC(O)NH_2$;

R^{22} is H, OH, NH_2 , SH, SCH_3 , SCH_2CH_3 , SCH_2CCH , SCH_2CHCH_2 , SC_3H_7 , $NH(CH_3)$, $N(CH_3)_2$, $NH(CH_2CH_3)$, $N(CH_2CH_3)_2$, $NH(CH_2CCH)$, $NH(CH_2CHCH_2)$, $NH(C_3H_7)$ or halogen (F, Cl, Br or I);

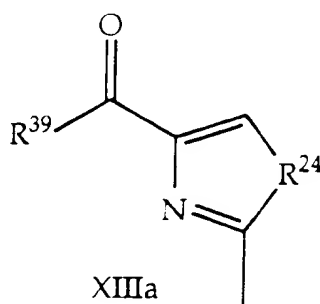
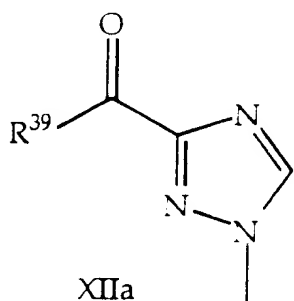
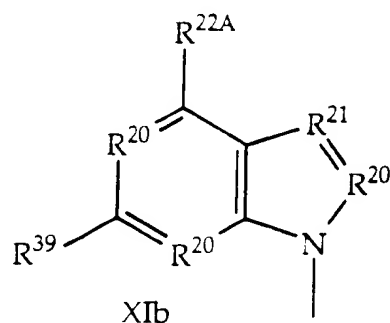
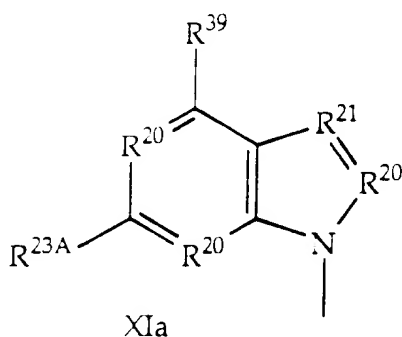
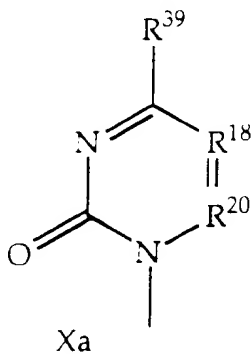
R^{23} is H, OH, F, Cl, Br, I, SCH_3 , SCH_2CH_3 , SCH_2CCH , SCH_2CHCH_2 , SC_3H_7 , OR^{16} , NH_2 , or NHR^{17} ; and

R^{24} is O, S or Se.

B includes both protected and unprotected forms of the heterocyclic bases. Protecting groups for exocyclic amines and other groups are known (Greene and include N-benzoyl, isobutyryl, 4,4'-dimethoxytrityl (DMT) and the like. The selection of a protecting group will be apparent to the ordinary artisan and will depend on the nature of the labile group and the chemistry

which the protecting group is expected to encounter, e.g., acidic, basic, oxidative, reductive or other conditions.

As used herein, B¹ is a protected heterocyclic base having the formula Xa, XIa, XIb, XIIa or XIIIa



15 wherein R¹⁸, R²⁰, R²¹, R²⁴ have the meanings previously defined; R^{22A} is R³⁹ or R²² provided that R²² is not NH₂; R^{23A} is R³⁹ or R²³ provided that R²³ is not NH₂; R³⁹ is NHR⁴⁰, NHC(O)R³⁶ or NCR⁴¹N(R³⁸)₂ wherein R³⁶ is C₁-C₁₉ alkyl, C₁-C₁₉ alkenyl, C₃-C₁₀ aryl, adamantoyl, alkylanyl, or C₃-C₁₀ aryl unsubstituted or substituted with 1 or 2 atoms or groups selected from
 20 halogen, methyl, ethyl, methoxy, ethoxy, hydroxy and cyano; R³⁸ is C₁-C₁₀ alkyl, or both R³⁸ together are 1-morpholino, 1-piperidine or 1-pyrrolidine; and R⁴¹ is hydrogen or CH₃. For heterocyclic bases of structures XIa and XIb, if R³⁹ is present at R^{22A} or R^{23A}, both R³⁹ groups on the same heterocyclic base will generally be the same. Exemplary R⁴⁰ include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, octyl, decanyl, lauryl and hexadecyl).

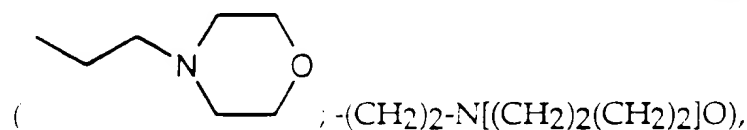
Specific heterocyclic bases include hypoxanthine, inosine, thymine, uracil, xanthine, 8-aza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-

1 amino-6-chloropurine, hypoxanthine, inosine and xanthine; 7-deaza-8-aza-
2 derivatives of adenine, guanine, 2-aminopurine, 2,6-diaminopurine, 2-
amino-6-chloropurine, hypoxanthine, inosine and xanthine; 1-deaza
derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine,
5 hypoxanthine, inosine and xanthine; 7-deaza derivatives of 2-aminopurine,
2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and
xanthine; 3-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-
amino-6-chloropurine, hypoxanthine, inosine and xanthine; 6-azacytosine; 5-
fluorocytosine; 5-chlorocytosine; 5-iodocytosine; 5-bromocytosine; 5-
10 methylcytosine; 5-bromovinyluracil; 5-fluorouracil; 5-chlorouracil; 5-
iodouracil; 5-bromouracil; 5-trifluoromethyluracil; 5-methoxymethyluracil; 5-
ethynyluracil; 5-propynyluracil and the like.

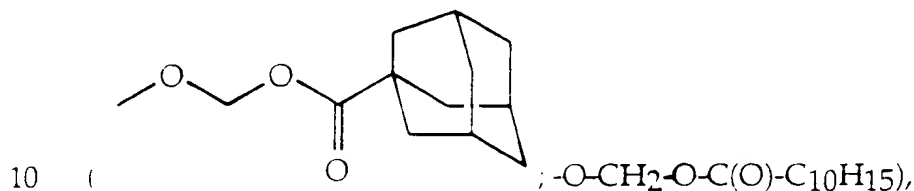
Preferably, B is a 9-purinyl residue selected from guanylyl, 3-deazaguanylyl,
1-deazaguanylyl, 8-azaguanylyl, 7-deazaguanylyl, adenyl, 3-deazaadenyl, 1-
15 dezazaadenyl, 8-azaadenyl, 7-deazaadenyl, 2,6-diaminopurinyl, 2-
aminopurinyl, 6-chloro-2-aminopurinyl and 6-thio-2-aminopurinyl, or a B is
a 1-pyrimidinyl residue selected from cytosinyl, 5-halocytosinyl, and 5-(C₁-C₃-
alkyl)cytosinyl.

The invention compounds, such as those of the formulas (L¹)(RO)P(O)-
20 Z-B, are optionally esterified at the phosphorus atom by the group R defined
above. Exemplary R groups include phenyl, 2- and 3-pyrrolyl, 2- and 3-
thienyl, 2- and 4-imidazolyl, 2-, 4- and 5-oxazolyl, 3- and 4-isoxazolyl, 2-, 4- and
5-thiazolyl, 3-, 4- and 5-isothiazolyl, 3- and 4-pyrazolyl, 2-, 3- and 4-pyridinyl,
2-, 4- and 5-pyrimidinyl, 2-, 3- and 4-alkoxyphenyl (C₁-C₁₂ alkyl including 2-, 3-
25 and 4-methoxyphenyl and 2-, 3- and 4-ethoxyphenyl), 2-, 3- and 4-halophenyl
(including 2-, 3- and 4-fluorophenyl), 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-
dihalophenyl (including 2,4-difluorophenyl and 2,4-dichlorophenyl), 2-, 3-
and 4-haloalkylphenyl (1 to 5 halogen atoms, C₁-C₁₂ alkyl including 2-, 3- and
4-trifluoromethylphenyl and 2-, 3- and 4-trichloromethylphenyl), 2-, 3- and 4-
30 cyanophenyl, carboalkoxyphenyl (C₁-C₄ alkyl including 2-, 3- and 4-
carboethoxyphenyl (-C₆H₄-C(O)-OC₂H₅) and 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-
dicarboethoxyphenyl), 1-, 2-, 3-, and 4-pyridinyl (-C₅H₄N), 2-, 3- and 4-
nitrophenyl, 2-, 3- and 4-haloalkylbenzyl (1 to 5 halogen atoms, C₁-C₁₂ alkyl
including 4-trifluoromethylbenzyl), alkylsalicylphenyl (C₁-C₄ alkyl including
35 ~~2-, 3- and 4-ethylsalicylphenyl, 2,3- and 4-acetylphenyl, 1,8-dihydroxy-~~

~~napththyl (-O-C₁₀H₆-OH or -O-C₁₀H₆-O-), 2,2'-dihydroxybiphenyl (-O-C₆H₄-C₆H₄-O-; both oxygen atoms are linked to the phosphorus atom), alkoxy ethyl [C₁-C₆ alkyl including -CH₂-CH₂-O-CH₃ (methoxy ethyl) and phenoxymethyl], aryloxy ethyl [C₆-C₉ aryl (including phenoxy ethyl) or C₆-C₉ aryl substituted by OH, NH₂, halo, C₁-C₄ alkyl or C₁-C₄ alkyl substituted by OH or by 1 to 3 halo atoms], -C₆H₄-CH₂-N(CH₃)₂, N-ethylmorpholino~~



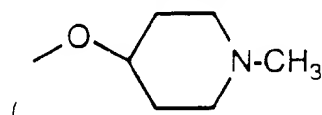
adamantoyl oxymethyl, pivaloyloxy(methoxyethyl)methyl (-CH(CH₂CH₂OCH₃)-O-C(O)-C(CH₃)₃),



pivaloyloxymethyl (-CH₂-O-C(O)-C(CH₃)₃), pivaloyloxy(methoxymethyl)methyl (-CH(CH₂OCH₃)-O-C(O)-C(CH₃)₃), pivaloyloxyisobutyl (-CH(CH(CH₃)₂)-O-C(O)-C(CH₃)₃) isobutyryloxymethyl (-CH₂-O-C(O)-CH₂-CH(CH₃)₂), cyclohexanoyl oxymethyl (-CH₂-O-C(O)-C₆H₁₁), phenyl (-C₆H₅),
 15 benzyl (-CH₂-C₆H₅), isopropyl (-CH(CH₃)₂), t-butyl (-C(CH₃)₃), -CH₂-CH₃, -(CH₂)₂-CH₃, -(CH₂)₃-CH₃, -(CH₂)₄-CH₃, -(CH₂)₅-CH₃, -CH₂-CH₂F, -CH₂-CH₂Cl, -CH₂-CF₃, -CH₂-CCl₃, R⁵, NHR^{6A} or N(R^{6A})₂ wherein R⁵ is CH₂C(O)N(R^{6A})₂, CH₂C(O)OR^{6A}, CH₂OC(O)R^{6A}, CH(R^{6A})OC(O)R^{6A}, CH₂C(R^{6A})₂CH₂OH, CH₂OR^{6A}, NH-CH₂-C(O)O-CH₂CH₃, N(CH₃)-CH₂-C(O)O-CH₂CH₃, NHR⁴⁰, CH₂-O-C(O)-C₆H₅, CH₂-O-C(O)-C₁₀H₁₅, -CH₂-O-C(O)-CH₂CH₃, CH₂-O-C(O)-CH(CH₃)₂, CH₂-O-C(O)-C(CH₃)₃, CH₂-O-C(O)-CH₂-C₆H₅, wherein R^{6A} is C₁-C₂₀ alkyl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N and halogen (1 to 5 halogen atoms), C₆-C₂₀ aryl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N and halogen (1 to 5 halogen atoms) or C₇-C₂₀ aryl-alkyl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N and halogen (1 to 5 halogen atoms), provided that for compounds of formulas N(R^{6A})₂, CH₂C(O)N(R^{6A})₂, CH₂C(O)OR^{6A},
 20 CH₂OC(O)R^{6A}, CH(R^{6A})OC(O)R^{6A} and CH₂C(R^{6A})₂CH₂OH, the total
 30 ~~CH₂OC(O)R^{6A}, CH(R^{6A})OC(O)R^{6A} and CH₂C(R^{6A})₂CH₂OH, the total~~

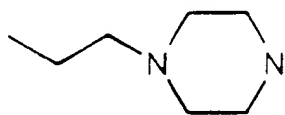
~~number of carbon atoms present is less than 25 (preferably the number of~~
carbon atoms present is about 4 to about 14) and R⁴⁰ is C₁-C₂₀ alkyl.

The invention compounds are optionally alkylated at the α-nitrogen
atom of the amino acid by the R¹ group defined above. Exemplary R¹ groups
5 include H, CH₃, CH₂CH₃, benzyl, 4-O-N-methylpiperidinyl



(
; -O-CH[(CH₂)₂(CH₂)₂N(CH₃)], 3-O-N-
methylpiperidinyl and the like.

The invention compounds are optionally esterified at the amino acid
carboxyl moiety by the R⁴ group defined above. Exemplary R⁴ groups include
10 H, methyl, ethyl, propyl, isopropyl, butyl, t-butyl (C(CH₃)₃), phenyl (-C₆H₅),
benzyl (-CH₂-C₆H₅), 1-pyridyl, 3-pyridyl, 1-pyrimidinyl, N-ethylmorpholino (-
CH₂-CH₂-N[(CH₂)₂(CH₂)₂O]), N-2-propylmorpholino (-CH(CH₃)-CH₂-
N[(CH₂)₂(CH₂)₂O]), methoxyethyl (-CH₂-CH₂-O-CH₃), 4-N-methylpiperidyl (-
CH[(CH₂)₂(CH₂)₂N(CH₃)], 3-N-methylpiperidyl, phenol which is 2-, 3-, or 4-
15 substituted by N(R³⁰)₂ where R³⁰ is independently H or C₁-C₆ alkyl
unsubstituted or substituted by substituents independently selected from the
group consisting of OH, O, N, COOR⁴ and halogen or C₆-C₁₂ aryl
unsubstituted or substituted by substituents independently selected from the
group consisting of OH, O, N, COOR⁴, N(R⁷)₂ and halogen (including 2-, 3-,
20 and 4-N,N-dimethylaminophenol and 2-, 3-, and 4-N,N-diethylamino-
phenol), 1-ethylpiperazinyl



[
; -CH₂-CH₂-NC₄H₈NH], and N⁴-substituted 1-ethyl-
piperazinyl (- (CH₂)₂-N[(CH₂)₂(CH₂)₂]NR², where R² is as defined above).

Additional compounds that are included in the invention are
25 nucleotide analog dimers that are linked via an amino or carboxyl group. As
used herein, dimers (or trimers) refer to the presence of two (or three)
nucleoside residues that comprise a compound. Thus, a -L¹-P(O)(L¹)-Z-B or
-P(O)(L¹)-Z-B radical covalently linked to a -L¹-P(O)(L¹)-Z-B or -P(O)(L¹)-Z-B
radical gives B-Z-P(O)(L¹)-P(O)(L¹)-Z-B, B-Z-P(O)(L¹)-L¹-P(O)(L¹)-Z-B or B-Z-
30 ~~P(O)(L¹)-L¹-L¹-P(O)(L¹)-Z-B.~~

Dimer nucleotide analogs are conveniently linked via amino acids, diamino acids, dicarboxylic amino acids, diamines or dicarboxylic acids such as β -aminoalanine, diaminobutyric acid, citrulline, homoarginine, homocitrulline, ornithine, γ -aminobutyric acid, arginine, histidine, asparagine, glutamine, β -hydroxyaspartic acid, β -hydroxyglutamic acid, β -methylaspartic acid, β -methylglutamic acid, 3-aminoadipic acid, 2-aminopimelic acid, 2-aminosuberic acid, β -amino acid analogs of lysine ($\text{NH}_2\text{-(CH}_2\text{)}_3\text{-CH(NH}_2\text{)-CH}_2\text{-CH-C(O)OH}$), arginine, histidine, asparagine, glutamine and the like. Exemplary compounds include dimers linked via lysine or β -lysine having the formulas $\text{B-Z-P(O)(L)-NH-(CH}_2\text{)}_4\text{-CH(C(O)OR}^4\text{)-NR}^1\text{-P(O)(L)-Z-B}$ and $\text{B-Z-P(O)(L)-NH-(CH}_2\text{)}_3\text{-CH(CH}_2\text{C(O)OR}^4\text{)-NR}^1\text{-P(O)(L)-Z-B}$ and dimers linked via aspartic or glutamic acid having the formula $\text{B-Z-P(O)(L)-O-C(O)-(CH}_2\text{)}_{1-2}\text{-CH(C(O)OR}^4\text{)-NR}^1\text{-P(O)(L)-Z-B}$. L, Z and B are independently selected.

Nucleotide analogs comprising dipeptidyl or tripeptidyl L groups are also included in the compounds of the invention. Nucleotide radicals are linked through side chain groups (usually amino or carboxyl) or through amino and carboxyl groups of the amino acids. Exemplary dipeptidyl and tripeptidyl dimers and trimers include compounds of the formulas $\text{B-Z-P(O)(L}^1\text{)-O-C(O)-(CR}^2\text{R}^3\text{)}_n\text{-NR}^1\text{-C(O)-(CR}^2\text{R}^3\text{)}_n\text{-NR}^1\text{-P(O)(L}^1\text{)-Z-B}$, $\text{B-Z-P(O)(L}^1\text{)-O-C(O)-(CR}^2\text{R}^3\text{)}_n\text{-NR}^1\text{-C(O)-(CR}^2\text{R}^3\text{)}_n\text{-NR}^1\text{-O-C(O)-(CR}^2\text{R}^3\text{)}_n\text{-NR}^1\text{-P(O)(L}^1\text{)-Z-B}$, $\text{B-Z-P(O)(L}^1\text{)-O-C(O)-CR}^2\text{(R}^3\text{-P(O)(L}^1\text{)-Z-B)-NR}^1\text{-C(O)-(CR}^2\text{R}^3\text{)}_n\text{-NR}^1\text{-P(O)(L}^1\text{)-Z-B}$ and $\text{B-Z-P(O)(L}^1\text{)-O-C(O)-(CR}^2\text{R}^3\text{)}_n\text{-NR}^1\text{-C(O)-CR}^2\text{(R}^3\text{-P(O)(L}^1\text{)-Z-B)-NR}^1\text{-P(O)(L}^1\text{)-Z-B}$. In order to provide a compound with a desired molar ratio of one Z-B compared to a second Z-B, tetramer, pentamer and higher polymer forms can also be prepared where Z and/or B are independently chosen.

As used herein, and unless modified by the immediate context: 1) the term alkyl, alkenyl and alkynyl refer to straight chain, branched and cyclic residues. Thus, $\text{C}_1\text{-C}_4$ alkyl includes methyl, ethyl, propyl, cyclopropyl, isopropyl, n-, sec-, iso- and tert-butyl, cyclobutyl and the like while alkenyl includes ethenyl, propenyl, isopropenyl, 1-, 2- and 3-butenyl, 1- and 2-isobutenyl and the like. The term alkyl also includes cyclic N-, S- or O-heterocarbonyl (such as piperidyl and morpholino). 2) The term aryl includes N-, S- or O- heteroaryl, including phenyl, 2- and 3-pyrrolyl, 2- and 3-thienyl, 2-

and 4-imidazolyl, 2-, 4- and 5-oxazolyl, 3- and 4-isoxazolyl, 2-, 4- and 5-thiazolyl, 3-, 4- and 5-isothiazolyl, 3- and 4-pyrazolyl, 2-, 3- and 4-pyridinyl, 2-, 4- and 5-pyrimidinyl. When "O" or "N" are substituted into aryl or alkyl this means that a ring or chain methyne or methylene is replaced by O, N or NH as the case may be. The term acyl means $R^X-C(O)-$, acyloxy means $R^X-C(O)-O-$, acyloxymethyl means $R^X-C(O)-O-CH_2-$ and thus, for example, C_{3-6} acyloxymethyl means $R^X-C(O)-O-CH_2-$ wherein R^X is a 1 to 4 carbon alkyl or aryl group (substituted or unsubstituted).

Nucleoside Phosphonates. Table 1 lists a group of exemplary nucleotide analogs of formula I having the structure $(L^1)(L^2)P(O)-Z-B$. These compounds generally have L^1 and L^2 groups that, when amino acids, are identical, although one of the amino acid groups can be different or replaced by another hydrolyzable group such as $-O-CH_2-O-C(O)-C(CH_3)_3$ or $-O-C_6H_5$ as listed below.

TABLE 1

L^1, L^2^*	$-Z-B^{**}$
1 -NH-CH ₂ -C(O)-OR ⁴	1 -CH ₂ -O-CH ₂ -CH ₂ -B
2 -NH-CH(CH ₃)-C(O)-OR ⁴	2 -CH ₂ -O-C [#] H(CH ₂ -OR ⁴)-CH ₂ -B
3 -NH-CH(CH ₃) ₂ -C(O)-OR ⁴	3 -CH ₂ -O-C [#] H(CH ₃)-CH ₂ -B
4 -NH-CH(CH(CH ₃) ₂)-C(O)-OR ⁴	4 -CH ₂ -O-C [#] H(CH ₂ F)-CH ₂ -B
5 -NH-CH(CH ₃)(CH ₃) ₂ -C(O)-OR ⁴	5 -CH ₂ -O-C [#] H(CH=CH ₂)-CH ₂ -B
6 -NH-CH ₂ -CH ₂ -CH ₂ -CH-C(O)-OR ⁴	6 -CH ₂ -O-C [#] H(CH ₂ N ₃)-CH ₂ -B
7 -NH-CH(CH ₂ -C ₆ H ₅)-C(O)-OR ⁴	7 ***
8 -NH-CH(CH ₂ -C ₈ NH ₆)-C(O)-OR ⁴	8 ****
9 -NH-CH(CH ₂ -CH ₂ -S-CH ₃)-C(O)-OR ⁴	
10 -NH-CH(CH ₂ OH)-C(O)-OR ⁴	
11 -NH-CH(CH(OH)(CH ₃)-C(O)-OR ⁴	
12 -NH-CH(-CH ₂ SH)-C(O)-OR ⁴	
13 -NH-CH(CH ₂ -C ₆ H ₅ OH)-C(O)-OR ⁴	
14 -NH-CH(CH ₂ -C(O)-NH ₂)-C(O)-OR ⁴	
15 -NH-CH(CH ₂ -CH ₂ -C(O)-NH ₂)-C(O)-OR ⁴	
16 -NH-CH(CH ₂ C(O)OR ⁴)-C(O)-OR ⁴	
17 -NH-CH(CH ₂ CH ₂ C(O)OR ⁴)-C(O)-OR ⁴	

- 18 -NH-CH(CH₂CH₂CH₂CH₂NH₂)-C(O)-OR⁴
- 19 -NH-CH(CH₂CH₂CH₂NHC(NH)(NH₂))-C(O)-OR⁴
- 20 -NH-CH(CH₂C₃N₂H₃)-C(O)-OR⁴
- 5 21 -NH-CH(CH₃)₂-CH₂-C(O)-OR⁴
- 22 -NH-CH₂-CH₂-C(O)-OR⁴
- 23 -NH-CH(CH₂-C₆H₅)-CH₂-C(O)-OR⁴
- 24 -NH-CH(CH₂CH₂CH₂NH₂)-CH₂-C(O)-OR⁴
- 25 -NH-CH(CH₂CH₂CH₂CH₂NH₂)-CH₂-C(O)-OR⁴
- 10 26 -NH-CH(CH₂CH₂NHC(NH)(NH₂))-CH₂-C(O)-OR⁴
- 27 -NH-CH(C(O)OR⁴)-CH₂-C(O)-OR⁴
- 28 -NH-CH(CH₂C(O)OR⁴)-CH₂-C(O)-OR⁴
- 29 -NH-CH(CH₂CH₂C(O)OR⁴)-CH₂-C(O)-OR⁴
- 30 -N(CH₃)-CH₂-C(O)-OR⁴
- 15 31 -NHR⁶
- 32 -O-CH₂-CH₂-N[CH₂]₂[CH₂]₂O
- 33 -O-CH₂-O-C(O)-C(CH₃)₃
- 34 -O-CH₂-O-C(O)-CH(CH₃)₂
- 35 -O-CH₂-O-C(O)-CH₂C₆H₄-O-CH₂CH₃
- 20 36 -O-CH₂-O-C(O)-C₁₀H₁₅
- 37 -O-CH₂-C₆H₅
- 38 -O-C₆H₅
- 39 -O-CH₂-C₆H₄N(CH₃)₂
- 40 -OH

25

B

- 1 adenin-9-yl
- 2 guanin-9-yl
- 3 cytosin-1-yl
- 30 4 2, 6-diaminopurin-9-yl
- 5 2-aminopurin-9-yl
- 6 6-azacytosin-1-yl
- 7 1-deazaadenin-9-yl
- 8 3-deazaadenin-9-yl
- 35 9 8-azaadenin-9-yl
- 10 7-deaza-8-azaadenin-9-yl

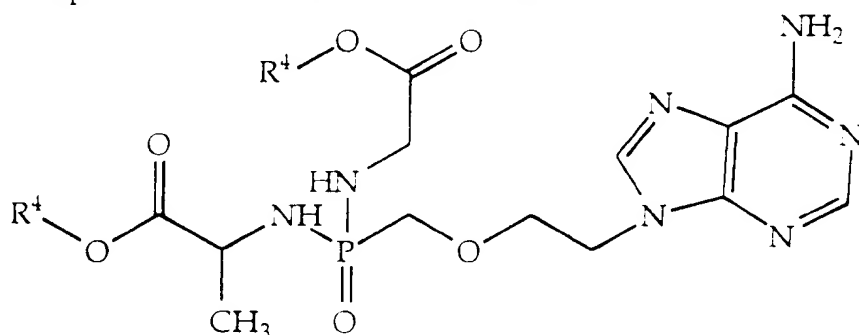
* - R⁴ includes H, propyl, isopropyl, t-butyl, phenyl, benzyl, 1-pyridinyl, 1-pyrimidinyl, N-ethylmorpholino, methoxyethyl, 4-hydroxy-N-methylpiperidinyl, 3-hydroxy-N-methylpiperidinyl, 1-ethylpiperazinyl; atoms with unfilled valences are linked to each other.

** - The carbon atom on the left of each structure is attached to the phosphorus atom; # - carbon atom having linked substituents in the *R*, *S* or *RS* configuration.

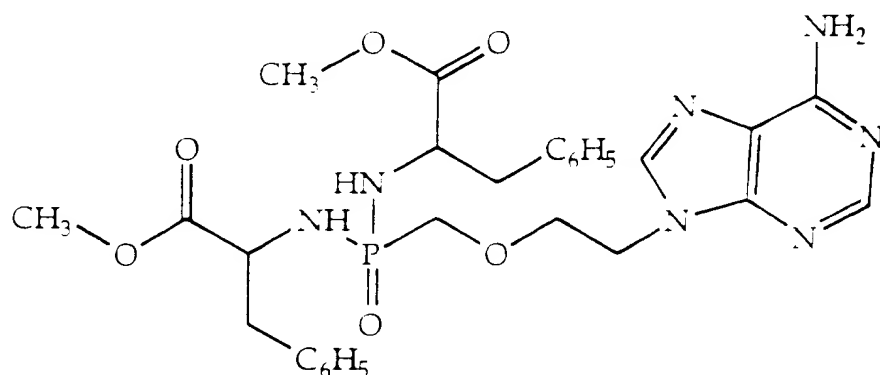
*** - Z-B substructure 7 is of formula V where R²⁵ and R²⁹ are O and B is thymine-1-yl (base 11) or one of the heterocyclic bases listed (1-10).

**** - Z-B substructure 8 is of formula IV where R²⁵ and R²⁹ are O, R²⁶ is S, R²⁷ is absent, R²⁸ is H and B is thymine-1-yl (base 11) or one of the heterocyclic bases listed (1-10) and includes the (+) and (-) enantiomers.

Compounds listed in Table 1 are designated herein by numbers assigned to L¹, L², Z and B according to the following convention, L¹.L².Z.B. Thus, compound 1.2.1.1, where R⁴ is benzyl, represents L¹ structure 1 (-NH-CH₂-C(O)-O-CH₂-C₆H₅), L² structure 2 (-NH-CH(CH₃)-C(O)-O-CH₂-C₆H₅), Z structure 1 (-CH₂-O-CH₂-CH₂-) and B structure 1 (adenine-9-yl). This compound would have the structure



which corresponds to the compound designated herein bis(alanyl benzyl ester)PMEA. Similarly, for the compound 7.7.1.1, L¹ structure 7 (NH-CH(CH₂-C₆H₅)-C(O)-OR⁴), L² structure 7 (NH-CH(CH₂-C₆H₅)-C(O)-OR⁴), Z structure 2 (-CH₂-O-CH₂-CH₂-) and B structure 1 (adenine-9-yl) would have, when R⁴ is methyl, the structure



and would represent the compound designated herein bis(phenylalanyl methyl ester)PMEA. Exemplary compounds include 1.1.1.1, 2.1.1.1, 3.1.1.1, 4.1.1.1, 5.1.1.1, 6.1.1.1, 7.1.1.1, 8.1.1.1, 9.1.1.1, 10.1.1.1, 11.1.1.1, 12.1.1.1, 13.1.1.1, 14.1.1.1, 15.1.1.1, 16.1.1.1, 17.1.1.1, 18.1.1.1, 19.1.1.1, 20.1.1.1, 21.1.1.1, 22.1.1.1, 23.1.1.1, 24.1.1.1, 25.1.1.1, 26.1.1.1, 27.1.1.1, 28.1.1.1, 29.1.1.1, 30.1.1.1, 31.1.1.1, 32.1.1.1, 33.1.1.1, 34.1.1.1, 35.1.1.1, 36.1.1.1, 37.1.1.1, 38.1.1.1, 39.1.1.1, 40.1.1.1, 1.2.1.1, 2.2.1.1, 3.2.1.1, 4.2.1.1, 5.2.1.1, 6.2.1.1, 7.2.1.1, 8.2.1.1, 9.2.1.1, 10.2.1.1, 11.2.1.1, 12.2.1.1, 13.2.1.1, 14.2.1.1, 15.2.1.1, 16.2.1.1, 17.2.1.1, 18.2.1.1, 19.2.1.1, 20.2.1.1, 21.2.1.1, 22.2.1.1, 23.2.1.1, 24.2.1.1, 25.2.1.1, 26.2.1.1, 27.2.1.1, 28.2.1.1, 29.2.1.1, 30.2.1.1, 31.2.1.1, 32.2.1.1, 33.2.1.1, 34.2.1.1, 35.2.1.1, 36.2.1.1, 37.2.1.1, 38.2.1.1, 39.2.1.1, 40.2.1.1, 1.3.1.1, 2.3.1.1, 3.3.1.1, 4.3.1.1, 5.3.1.1, 6.3.1.1, 7.3.1.1, 8.3.1.1, 9.3.1.1, 10.3.1.1, 11.3.1.1, 12.3.1.1, 13.3.1.1, 14.3.1.1, 15.3.1.1, 16.3.1.1, 17.3.1.1, 18.3.1.1, 19.3.1.1, 20.3.1.1, 21.3.1.1, 22.3.1.1, 23.3.1.1, 24.3.1.1, 25.3.1.1, 26.3.1.1, 27.3.1.1, 28.3.1.1, 29.3.1.1, 30.3.1.1, 31.3.1.1, 32.3.1.1, 33.3.1.1, 34.3.1.1, 35.3.1.1, 36.3.1.1, 37.3.1.1, 38.3.1.1, 39.3.1.1, 40.3.1.1, 1.4.1.1, 2.4.1.1, 3.4.1.1, 4.4.1.1, 5.4.1.1, 6.4.1.1, 7.4.1.1, 8.4.1.1, 9.4.1.1, 10.4.1.1, 11.4.1.1, 12.4.1.1, 13.4.1.1, 14.4.1.1, 15.4.1.1, 16.4.1.1, 17.4.1.1, 18.4.1.1, 19.4.1.1, 20.4.1.1, 21.4.1.1, 22.4.1.1, 23.4.1.1, 24.4.1.1, 25.4.1.1, 26.4.1.1, 27.4.1.1, 28.4.1.1, 29.4.1.1, 30.4.1.1, 31.4.1.1, 32.4.1.1, 33.4.1.1, 34.4.1.1, 35.4.1.1, 36.4.1.1, 37.4.1.1, 38.4.1.1, 39.4.1.1, 40.4.1.1, 1.5.1.1, 2.5.1.1, 3.5.1.1, 4.5.1.1, 5.5.1.1, 6.5.1.1, 7.5.1.1, 8.5.1.1, 9.5.1.1, 10.5.1.1, 11.5.1.1, 12.5.1.1, 13.5.1.1, 14.5.1.1, 15.5.1.1, 16.5.1.1, 17.5.1.1, 18.5.1.1, 19.5.1.1, 20.5.1.1, 21.5.1.1, 22.5.1.1, 23.5.1.1, 24.5.1.1, 25.5.1.1, 26.5.1.1, 27.5.1.1, 28.5.1.1, 29.5.1.1, 30.5.1.1, 31.5.1.1, 32.5.1.1, 33.5.1.1, 34.5.1.1, 35.5.1.1, 36.5.1.1, 37.5.1.1, 38.5.1.1, 39.5.1.1, 40.5.1.1, 1.6.1.1, 2.6.1.1, 3.6.1.1, 4.6.1.1, 5.6.1.1, 6.6.1.1, 7.6.1.1, 8.6.1.1, 9.6.1.1, 10.6.1.1, 11.6.1.1, 12.6.1.1, 13.6.1.1, 14.6.1.1, 15.6.1.1, 16.6.1.1, 17.6.1.1, 18.6.1.1, 19.6.1.1, 20.6.1.1, 21.6.1.1, 22.6.1.1, 23.6.1.1, 24.6.1.1, 25.6.1.1, 26.6.1.1, 27.6.1.1, 28.6.1.1, 29.6.1.1, 30.6.1.1, 31.6.1.1, 32.6.1.1, 33.6.1.1, 34.6.1.1, 35.6.1.1,

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 38.29.3.5, 39.29.3.5 and 40.29.3.5.

Table 2 lists a group of cyclic nucleotide analogs of structure I wherein
 25 Z forms a heterocyclic ring containing the phosphorus atom of the
 phosphonate group and two oxygen atoms as shown. Hydrolysis of the L¹
 group linked to the phosphorus atom and subsequent ring hydrolysis results
 in formation of an HPMP nucleoside such as HPMPC (1-(2-
 phosphonomethoxy-3-hydroxypropyl)-cytosine).

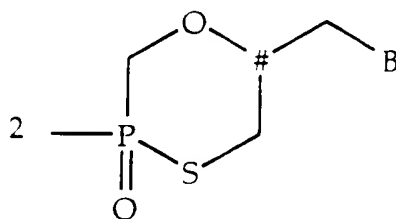
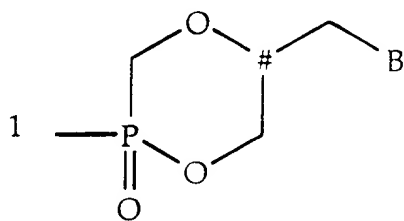
TABLE 2

L¹*

- 1 -NH-CH₂-C(O)-OR⁴
- 35 2 -NH-CH(CH₃)-C(O)-OR⁴
- 3 -NH-CH(CH₃)₂-C(O)-OR⁴

- 4 -NH-CH(CH(CH₃)₂)-C(O)-OR⁴
 5 -NH-CH(CH₃)(CH₃)₂-C(O)-OR⁴
 6 -N-CH₂-CH₂-CH₂-CH-C(O)-OR⁴
 7 -NH-CH(CH₂-C₆H₅)-C(O)-OR⁴
 5 8 -NH-CH(CH₂-C₈NH₆)-C(O)-OR⁴
 9 -NH-CH(CH₂-CH₂-S-CH₃)-C(O)-OR⁴
 10 -NH-CH(CH₂OH)-C(O)-OR⁴
 11 -NH-CH(CH(OH)(CH₃))-C(O)-OR⁴
 12 -NH-CH(-CH₂SH)-C(O)-OR⁴
 10 13 -NH-CH(CH₂-C₆H₅OH)-C(O)-OR⁴
 14 -NH-CH(CH₂-C(O)-NH₂)-C(O)-OR⁴
 15 -NH-CH(CH₂-CH₂-C(O)-NH₂)-C(O)-OR⁴
 16 -NH-CH(CH₂C(O)OR⁴)-C(O)-OR⁴
 17 -NH-CH(CH₂CH₂C(O)OR⁴)-C(O)-OR⁴
 15 18 -NH-CH(CH₂CH₂CH₂CH₂NH₂)-C(O)-OR⁴
 19 -NH-CH(CH₂CH₂CH₂NHC(NH)(NH₂))-C(O)-OR⁴
 20 -NH-CH(CH₂C₃N₂H₃)-C(O)-OR⁴
 21 -NH-CH(CH₂CH₂CH₂NH₂)-CH₂-C(O)-OR⁴
 22 -NH-CH(CH₂CH₂CH₂CH₂NH₂)-CH₂-C(O)-OR⁴
 20 23 -NH-CH(CH₂CH₂NHC(NH)(NH₂))-CH₂-C(O)-OR⁴
 24 -NH-CH(C(O)OR⁴)-CH₂-C(O)-OR⁴
 25 -NH-CH(CH₂C(O)OR⁴)-CH₂-C(O)-OR⁴
 26 -NH-CH(CH₂CH₂C(O)OR⁴)-CH₂-C(O)-OR⁴

25 Z-B**



B

1. adenin-9-yl
 2. guanin-9-yl
 30 3. cytosin-1-yl
 4. 2, 6-diaminopurin-9-yl

5. 2-aminopurin-9-yl

6. 6-azacytosin-1-yl

7. 1-deazaadenin-9-yl

8. 3-deazaadenin-9-yl

9. 8-azaadenin-9-yl

5 10. 7-deaza-8-azaadenin-9-yl

* - See Table 1 footnote.

** - See Table 1 footnote.

- See Table 1 footnote.

- 10 Compounds listed in Table 2 are designated herein by numbers assigned to L¹, Z and B according to the following convention, L.Z.B. Thus, compounds 1.1.3 and 1.2.3 represent, when R₄ is H, glycinyl cyclic HPMPC and alanyl cyclic HPMPC. Exemplary compounds include 1.1.1, 1.1.2, 1.1.3, 1.1.4, 1.1.5, 1.1.6, 1.1.7, 1.1.8, 1.1.9, 1.1.10, 2.1.1, 2.1.2, 2.1.3, 2.1.4, 2.1.5, 2.1.6, 2.1.7, 2.1.8, 2.1.9, 2.1.10, 3.1.1, 3.1.2, 3.1.3, 3.1.4, 3.1.5, 3.1.6, 3.1.7, 3.1.8, 3.1.9, 3.1.10, 4.1.1, 4.1.2, 4.1.3, 4.1.4, 4.1.5, 4.1.6, 4.1.7, 4.1.8, 4.1.9, 4.1.10, 5.1.1, 5.1.2, 5.1.3, 5.1.4, 5.1.5, 5.1.6, 5.1.7, 5.1.8, 5.1.9, 5.1.10, 6.1.1, 6.1.2, 6.1.3, 6.1.4, 6.1.5, 6.1.6, 6.1.7, 6.1.8, 6.1.9, 6.1.10, 7.1.1, 7.1.2, 7.1.3, 7.1.4, 7.1.5, 7.1.6, 7.1.7, 7.1.8, 7.1.9, 7.1.10, 8.1.1, 8.1.2, 8.1.3, 8.1.4, 8.1.5, 8.1.6, 8.1.7, 8.1.8, 8.1.9, 8.1.10, 9.1.1, 9.1.2, 9.1.3, 9.1.4, 9.1.5, 9.1.6, 9.1.7, 9.1.8, 9.1.9, 9.1.10, 10.1.1, 10.1.2, 10.1.3, 10.1.4, 10.1.5, 10.1.6, 10.1.7, 10.1.8, 10.1.9, 10.1.10, 11.1.1, 11.1.2, 11.1.3, 11.1.4, 11.1.5, 11.1.6, 11.1.7, 11.1.8, 11.1.9, 11.1.10, 12.1.1, 12.1.2, 12.1.3, 12.1.4, 12.1.5, 12.1.6, 12.1.7, 12.1.8, 12.1.9, 12.1.10, 13.1.1, 13.1.2, 13.1.3, 13.1.4, 13.1.5, 13.1.6, 13.1.7, 13.1.8, 13.1.9, 13.1.10, 14.1.1, 14.1.2, 14.1.3, 14.1.4, 14.1.5, 14.1.6, 14.1.7, 14.1.8, 14.1.9, 14.1.10, 15.1.1, 15.1.2, 15.1.3, 15.1.4, 15.1.5, 15.1.6, 15.1.7, 15.1.8, 15.1.9, 15.1.10, 16.1.1, 16.1.2, 16.1.3, 16.1.4, 16.1.5, 16.1.6, 16.1.7, 16.1.8, 16.1.9, 16.1.10, 17.1.1, 17.1.2, 17.1.3, 17.1.4, 17.1.5, 17.1.6, 17.1.7, 17.1.8, 17.1.9, 17.1.10, 18.1.1, 18.1.2, 18.1.3, 18.1.4, 18.1.5, 18.1.6, 18.1.7, 18.1.8, 18.1.9, 18.1.10, 19.1.1, 19.1.2, 19.1.3, 19.1.4, 19.1.5, 19.1.6, 19.1.7, 19.1.8, 19.1.9, 19.1.10, 20.1.1, 20.1.2, 20.1.3, 20.1.4, 20.1.5, 20.1.6, 20.1.7, 20.1.8, 20.1.9, 20.1.10, 21.1.1, 21.1.2, 21.1.3, 21.1.4, 21.1.5, 21.1.6, 21.1.7, 21.1.8, 21.1.9, 21.1.10, 22.1.1, 22.1.2, 22.1.3, 22.1.4, 22.1.5, 22.1.6, 22.1.7, 22.1.8, 22.1.9, 22.1.10, 23.1.1, 23.1.2, 23.1.3, 23.1.4, 23.1.5, 23.1.6, 23.1.7, 23.1.8, 23.1.9, 23.1.10, 24.1.1, 24.1.2, 24.1.3, 24.1.4, 24.1.5, 24.1.6, 24.1.7, 24.1.8, 24.1.9, 24.1.10, 25.1.1, 25.1.2, 25.1.3, 25.1.4, 25.1.5, 25.1.6, 25.1.7, 25.1.8, 25.1.9, 25.1.10, 26.1.1, 26.1.2, 26.1.3, 26.1.4, 26.1.5, 26.1.6, 26.1.7, 26.1.8, 26.1.9, 26.1.10, 27.1.1, 27.1.2, 27.1.3, 27.1.4, 27.1.5, 27.1.6, 27.1.7, 27.1.8, 27.1.9, 27.1.10, 28.1.1, 28.1.2, 28.1.3, 28.1.4, 28.1.5, 28.1.6, 28.1.7,

28.1.8, 28.1.9, 28.1.10, 1.2.1, 1.2.2, 1.2.3, 1.2.4, 1.2.5, 1.2.6, 1.2.7, 1.2.8, 1.2.9, 1.2.10, 2.2.1, 2.2.2, 2.2.3, 2.2.4, 2.2.5, 2.2.6, 2.2.7, 2.2.8, 2.2.9, 2.2.10, 3.2.1, 3.2.2, 3.2.3, 3.2.4, 3.2.5, 3.2.6, 3.2.7, 3.2.8, 3.2.9, 3.2.10, 4.2.1, 4.2.2, 4.2.3, 4.2.4, 4.2.5, 4.2.6, 4.2.7, 4.2.8, 4.2.9, 4.2.10, 5.2.1, 5.2.2, 5.2.3, 5.2.4, 5.2.5, 5.2.6, 5.2.7, 5.2.8, 5.2.9, 5.2.10, 6.2.1, 6.2.2, 5 6.2.3, 6.2.4, 6.2.5, 6.2.6, 6.2.7, 6.2.8, 6.2.9, 6.2.10, 7.2.1, 7.2.2, 7.2.3, 7.2.4, 7.2.5, 7.2.6, 7.2.7, 7.2.8, 7.2.9, 7.2.10, 8.2.1, 8.2.2, 8.2.3, 8.2.4, 8.2.5, 8.2.6, 8.2.7, 8.2.8, 8.2.9, 8.2.10, 9.2.1, 9.2.2, 9.2.3, 9.2.4, 9.2.5, 9.2.6, 9.2.7, 9.2.8, 9.2.9, 9.2.10, 10.2.1, 10.2.2, 10.2.3, 10.2.4, 10.2.5, 10.2.6, 10.2.7, 10.2.8, 10.2.9, 10.2.10, 11.2.1, 11.2.2, 11.2.3, 11.2.4, 11.2.5, 11.2.6, 11.2.7, 11.2.8, 11.2.9, 11.2.10, 12.2.1, 12.2.2, 12.2.3, 12.2.4, 12.2.5, 10 12.2.6, 12.2.7, 12.2.8, 12.2.9, 12.2.10, 13.2.1, 13.2.2, 13.2.3, 13.2.4, 13.2.5, 13.2.6, 13.2.7, 13.2.8, 13.2.9, 13.2.10, 14.2.1, 14.2.2, 14.2.3, 14.2.4, 14.2.5, 14.2.6, 14.2.7, 14.2.8, 14.2.9, 14.2.10, 15.2.1, 15.2.2, 15.2.3, 15.2.4, 15.2.5, 15.2.6, 15.2.7, 15.2.8, 15.2.9, 15.2.10, 16.2.1, 16.2.2, 16.2.3, 16.2.4, 16.2.5, 16.2.6, 16.2.7, 16.2.8, 16.2.9, 16.2.10, 17.2.1, 17.2.2, 17.2.3, 17.2.4, 17.2.5, 17.2.6, 17.2.7, 17.2.8, 17.2.9, 17.2.10, 15 18.2.1, 18.2.2, 18.2.3, 18.2.4, 18.2.5, 18.2.6, 18.2.7, 18.2.8, 18.2.9, 18.2.10, 19.2.1, 19.2.2, 19.2.3, 19.2.4, 19.2.5, 19.2.6, 19.2.7, 19.2.8, 19.2.9, 19.2.10, 20.2.1, 20.2.2, 20.2.3, 20.2.4, 20.2.5, 20.2.6, 20.2.7, 20.2.8, 20.2.9, 20.2.10, 21.2.1, 21.2.2, 21.2.3, 21.2.4, 21.2.5, 21.2.6, 21.2.7, 21.2.8, 21.2.9, 21.2.10, 22.2.1, 22.2.2, 22.2.3, 22.2.4, 22.2.5, 22.2.6, 22.2.7, 22.2.8, 22.2.9, 22.2.10, 23.2.1, 23.2.2, 23.2.3, 23.2.4, 23.2.5, 20 23.2.6, 23.2.7, 23.2.8, 23.2.9, 23.2.10, 24.2.1, 24.2.2, 24.2.3, 24.2.4, 24.2.5, 24.2.6, 24.2.7, 24.2.8, 24.2.9, 24.2.10, 25.2.1, 25.2.2, 25.2.3, 25.2.4, 25.2.5, 25.2.6, 25.2.7, 25.2.8, 25.2.9, 25.2.10, 26.2.1, 26.2.2, 26.2.3, 26.2.4, 26.2.5, 26.2.6, 26.2.7, 26.2.8, 26.2.9 and 26.2.10.

25 Table 3 lists a group of cyclic nucleotide analog amidates of structure I wherein L¹ forms a heterocyclic ring containing the phosphorus atom of the phosphonate group. Hydrolysis of the heterocyclic ring linked through the phosphorus atom results in formation of a phosphonate nucleotide analog such as HPMPC, PMEA, PMEG or PMPDAP depending on the Z group that is 30 present.

TABLE 3

L ¹	Z-B**
1 -NH-CH ₂ -C(O)-O-CH ₂ -O-	1 -CH ₂ -O-CH ₂ -CH ₂ -B
35 2 -NH-CH(CH ₃)-C(O)-O-CH ₂ -O-	2 -CH ₂ -O-C#H(CH ₂ -OR ⁴)-CH ₂ -B

- | | | |
|----|-----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| | 3 -NH-CH(CH ₃) ₂ -C(O)-O-CH ₂ -O- | 3 -CH ₂ -O-C#H(CH ₃)-CH ₂ -B |
| | 4 -NH-CH(CH(CH ₃) ₂)-C(O)-O-CH ₂ -O- | 4 -CH ₂ -O-C#H(CH ₂ F)-CH ₂ -B |
| | 5 -NH-CH(CH ₃)(CH ₃) ₂ -C(O)-O-CH ₂ -O- | 5 -CH ₂ -O-C#H(CH=CH ₂)-CH ₂ -B |
| 5 | 6 -NH-CH ₂ -CH ₂ -CH ₂ -CH-C(O)-O-CH ₂ -O- | 6 -CH ₂ -O-C#H(CH ₂ N ₃)-CH ₂ -B |
| | 7 -NH-CH(CH ₂ -C ₆ H ₅)-C(O)-O-CH ₂ -O- | |
| | 8 -NH-CH(CH ₂ -C ₈ NH ₆)-C(O)-O-CH ₂ -O- | |
| | 9 -NH-CH(CH ₂ -CH ₂ -S-CH ₃)-C(O)-O- | |
| | 10 -NH-CH(CH ₂ OH)-C(O)-O-CH ₂ -O- | |
| 10 | 11 -NH-CH(CH(OH)(CH ₃))-C(O)-O-CH ₂ -O- | |
| | 12 -NH-CH(-CH ₂ SH)-C(O)-O-CH ₂ -O- | |
| | 13 -NH-CH(CH ₂ -C ₆ H ₅ OH)-C(O)-O-CH ₂ -O- | |
| | 14 -NH-CH(CH ₂ -C(O)-NH ₂)-C(O)-O-CH ₂ -O- | |
| | 15 -NH-CH(CH ₂ -CH ₂ -C(O)-NH ₂)-C(O)-O-CH ₂ -O- | |
| 15 | 16 -NH-CH(CH ₂ C(O)OR ⁴)-C(O)-O-CH ₂ -O- | |
| | 17 -NH-CH(CH ₂ CH ₂ C(O)OR ⁴)-C(O)-O-CH ₂ -O- | |
| | 18 -NH-CH(CH ₂ CH ₂ CH ₂ CH ₂ NH ₂)-C(O)-O-CH ₂ -O- | |
| | 19 -NH-CH(CH ₂ CH ₂ CH ₂ NHC(NH)(NH ₂))-C(O)-O-CH ₂ -O- | |
| | 20 -NH-CH(CH ₂ C ₃ N ₂ H ₃)-C(O)-O-CH ₂ -O- | |
| 20 | 21 -NH-CH(CH ₂ CH ₂ CH ₂ NH ₂)-CH ₂ -C(O)-O-CH ₂ -O- | |
| | 22 -NH-CH(CH ₂ CH ₂ CH ₂ CH ₂ NH ₂)-CH ₂ -C(O)-O-CH ₂ -O- | |
| | 23 -NH-CH(CH ₂ CH ₂ NHC(NH)(NH ₂))-CH ₂ -C(O)-O-CH ₂ -O- | |
| | 24 -NH-CH(C(O)OR ⁴)-CH ₂ -C(O)-O-CH ₂ -O- | |
| | 25 -NH-CH(CH ₂ C(O)OR ⁴)-CH ₂ -C(O)-O- | |
| 25 | 26 -NH-CH(CH ₂ CH ₂ C(O)OR ⁴)-CH ₂ -C(O)-O-CH ₂ -O- | |
| | 27 -NH-CH ₂ -C(O)-O-CH(C(O)OR ⁴)-N- | |
| | 28 -NH-CH(CH ₃)-C(O)-O-CH(C(O)OR ⁴)-N- | |

B

- | | | |
|----|---|------------------------|
| 30 | 1 | adenin-9-yl |
| | 2 | guanin-9-yl |
| | 3 | cytosin-1-yl |
| | 4 | 2, 6-diaminopurin-9-yl |
| | 5 | 2-aminopurin-9-yl |
| 35 | 6 | 6-azacytosin-1-yl |
| | 7 | 1-deazaadenin-9-yl |

- 8 3-deazaadenin-9-yl
- 9 8-azaadenin-9-yl
- 10 7-deaza-8-azaadenin-9-yl

5 * - See Table 1 footnote; the terminal nitrogen and oxygen or nitrogen atoms are both linked to the phosphorus atom of the phosphonate group.

** - See Table 1 footnote.

- See Table 1 footnote.

- 10 Compounds listed in Table 3 are designated herein by numbers assigned to L¹, Z and B according to the following convention, L¹.Z.B. Thus, compounds 1.1.1 and 2.3.4 represent compounds designated cyclic glycinyIPMEA and cyclic alanylPMPDAP. Exemplary compounds include 1.1.1, 1.1.2, 1.1.3, 1.1.4, 1.1.5, 1.1.6, 1.1.7, 1.1.8, 1.1.9, 1.1.10, 2.1.1, 2.1.2, 2.1.3, 2.1.4, 2.1.5, 2.1.6, 2.1.7, 2.1.8, 2.1.9, 2.1.10, 3.1.1, 3.1.2, 3.1.3, 3.1.4, 3.1.5, 3.1.6, 3.1.7, 3.1.8, 3.1.9, 3.1.10, 4.1.1, 4.1.2, 4.1.3, 4.1.4, 4.1.5, 4.1.6, 4.1.7, 4.1.8, 4.1.9, 4.1.10, 5.1.1, 5.1.2, 5.1.3, 5.1.4, 5.1.5, 5.1.6, 5.1.7, 5.1.8, 5.1.9, 5.1.10, 6.1.1, 6.1.2, 6.1.3, 6.1.4, 6.1.5, 6.1.6, 6.1.7, 6.1.8, 6.1.9, 6.1.10, 7.1.1, 7.1.2, 7.1.3, 7.1.4, 7.1.5, 7.1.6, 7.1.7, 7.1.8, 7.1.9, 7.1.10, 8.1.1, 8.1.2, 8.1.3, 8.1.4, 8.1.5, 8.1.6, 8.1.7, 8.1.8, 8.1.9, 8.1.10, 9.1.1, 9.1.2, 9.1.3, 9.1.4, 9.1.5, 9.1.6, 9.1.7, 9.1.8, 9.1.9, 9.1.10, 10.1.1, 10.1.2, 10.1.3, 10.1.4, 10.1.5, 10.1.6, 10.1.7, 10.1.8, 10.1.9, 10.1.10, 11.1.1, 11.1.2, 11.1.3, 11.1.4, 11.1.5, 11.1.6, 11.1.7, 11.1.8, 11.1.9, 11.1.10, 12.1.1, 12.1.2, 12.1.3, 12.1.4, 12.1.5, 12.1.6, 12.1.7, 12.1.8, 12.1.9, 12.1.10, 13.1.1, 13.1.2, 13.1.3, 13.1.4, 13.1.5, 13.1.6, 13.1.7, 13.1.8, 13.1.9, 13.1.10, 14.1.1, 14.1.2, 14.1.3, 14.1.4, 14.1.5, 14.1.6, 14.1.7, 14.1.8, 14.1.9, 14.1.10, 15.1.1, 15.1.2, 15.1.3, 15.1.4, 15.1.5, 15.1.6, 15.1.7, 15.1.8, 15.1.9, 15.1.10, 16.1.1, 16.1.2, 16.1.3, 16.1.4, 16.1.5, 16.1.6, 16.1.7, 16.1.8, 16.1.9, 16.1.10, 17.1.1, 17.1.2, 17.1.3, 17.1.4, 17.1.5, 17.1.6, 17.1.7, 17.1.8, 17.1.9, 17.1.10, 18.1.1, 18.1.2, 18.1.3, 18.1.4, 18.1.5, 18.1.6, 18.1.7, 18.1.8, 18.1.9, 18.1.10, 19.1.1, 19.1.2, 19.1.3, 19.1.4, 19.1.5, 19.1.6, 19.1.7, 19.1.8, 19.1.9, 19.1.10, 20.1.1, 20.1.2, 20.1.3, 20.1.4, 20.1.5, 20.1.6, 20.1.7, 20.1.8, 20.1.9, 20.1.10, 21.1.1, 21.1.2, 21.1.3, 21.1.4, 21.1.5, 21.1.6, 21.1.7, 21.1.8, 21.1.9, 21.1.10, 22.1.1, 22.1.2, 22.1.3, 22.1.4, 22.1.5, 22.1.6, 22.1.7, 22.1.8, 22.1.9, 22.1.10, 23.1.1, 23.1.2, 23.1.3, 23.1.4, 23.1.5, 23.1.6, 23.1.7, 23.1.8, 23.1.9, 23.1.10, 24.1.1, 24.1.2, 24.1.3, 24.1.4, 24.1.5, 24.1.6, 24.1.7, 24.1.8, 24.1.9, 24.1.10, 25.1.1, 25.1.2, 25.1.3, 25.1.4, 25.1.5, 25.1.6, 25.1.7, 25.1.8, 25.1.9, 25.1.10, 26.1.1, 26.1.2, 26.1.3, 26.1.4, 26.1.5, 26.1.6, 26.1.7, 26.1.8, 26.1.9, 26.1.10, 27.1.1, 27.1.2, 27.1.3, 27.1.4, 27.1.5,

27.1.6, 27.1.7, 27.1.8, 27.1.9, 27.1.10, 28.1.1, 28.1.2, 28.1.3, 28.1.4, 28.1.5, 28.1.6,
 28.1.7, 28.1.8, 28.1.9, 28.1.10, 1.2.1, 1.2.2, 1.2.3, 1.2.4, 1.2.5, 1.2.6, 1.2.7, 1.2.8, 1.2.9,
 1.2.10, 2.2.1, 2.2.2, 2.2.3, 2.2.4, 2.2.5, 2.2.6, 2.2.7, 2.2.8, 2.2.9, 2.2.10, 3.2.1, 3.2.2, 3.2.3,
 3.2.4, 3.2.5, 3.2.6, 3.2.7, 3.2.8, 3.2.9, 3.2.10, 4.2.1, 4.2.2, 4.2.3, 4.2.4, 4.2.5, 4.2.6, 4.2.7,
 5 4.2.8, 4.2.9, 4.2.10, 5.2.1, 5.2.2, 5.2.3, 5.2.4, 5.2.5, 5.2.6, 5.2.7, 5.2.8, 5.2.9, 5.2.10, 6.2.1,
 6.2.2, 6.2.3, 6.2.4, 6.2.5, 6.2.6, 6.2.7, 6.2.8, 6.2.9, 6.2.10, 7.2.1, 7.2.2, 7.2.3, 7.2.4, 7.2.5,
 7.2.6, 7.2.7, 7.2.8, 7.2.9, 7.2.10, 8.2.1, 8.2.2, 8.2.3, 8.2.4, 8.2.5, 8.2.6, 8.2.7, 8.2.8, 8.2.9,
 8.2.10, 9.2.1, 9.2.2, 9.2.3, 9.2.4, 9.2.5, 9.2.6, 9.2.7, 9.2.8, 9.2.9, 9.2.10, 10.2.1, 10.2.2,
 10.2.3, 10.2.4, 10.2.5, 10.2.6, 10.2.7, 10.2.8, 10.2.9, 10.2.10, 11.2.1, 11.2.2, 11.2.3,
 10 11.2.4, 11.2.5, 11.2.6, 11.2.7, 11.2.8, 11.2.9, 11.2.10, 12.2.1, 12.2.2, 12.2.3, 12.2.4,
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 13.2.6, 13.2.7, 13.2.8, 13.2.9, 13.2.10, 14.2.1, 14.2.2, 14.2.3, 14.2.4, 14.2.5, 14.2.6,
 14.2.7, 14.2.8, 14.2.9, 14.2.10, 15.2.1, 15.2.2, 15.2.3, 15.2.4, 15.2.5, 15.2.6, 15.2.7,
 15.2.8, 15.2.9, 15.2.10, 16.2.1, 16.2.2, 16.2.3, 16.2.4, 16.2.5, 16.2.6, 16.2.7, 16.2.8,
 15 16.2.9, 16.2.10, 17.2.1, 17.2.2, 17.2.3, 17.2.4, 17.2.5, 17.2.6, 17.2.7, 17.2.8, 17.2.9,
 17.2.10, 18.2.1, 18.2.2, 18.2.3, 18.2.4, 18.2.5, 18.2.6, 18.2.7, 18.2.8, 18.2.9, 18.2.10,
 19.2.1, 19.2.2, 19.2.3, 19.2.4, 19.2.5, 19.2.6, 19.2.7, 19.2.8, 19.2.9, 19.2.10, 20.2.1,
 20.2.2, 20.2.3, 20.2.4, 20.2.5, 20.2.6, 20.2.7, 20.2.8, 20.2.9, 20.2.10, 21.2.1, 21.2.2,
 21.2.3, 21.2.4, 21.2.5, 21.2.6, 21.2.7, 21.2.8, 21.2.9, 21.2.10, 22.2.1, 22.2.2, 22.2.3,
 20 22.2.4, 22.2.5, 22.2.6, 22.2.7, 22.2.8, 22.2.9, 22.2.10, 23.2.1, 23.2.2, 23.2.3, 23.2.4,
 23.2.5, 23.2.6, 23.2.7, 23.2.8, 23.2.9, 23.2.10, 24.2.1, 24.2.2, 24.2.3, 24.2.4, 24.2.5,
 24.2.6, 24.2.7, 24.2.8, 24.2.9, 24.2.10, 25.2.1, 25.2.2, 25.2.3, 25.2.4, 25.2.5, 25.2.6,
 25.2.7, 25.2.8, 25.2.9, 25.2.10, 26.2.1, 26.2.2, 26.2.3, 26.2.4, 26.2.5, 26.2.6, 26.2.7,
 26.2.8, 26.2.9, 26.2.10, 27.2.1, 27.2.2, 27.2.3, 27.2.4, 27.2.5, 27.2.6, 27.2.7, 27.2.8,
 25 27.2.9, 27.2.10, 28.2.1, 28.2.2, 28.2.3, 28.2.4, 28.2.5, 28.2.6, 28.2.7, 28.2.8, 28.2.9,
 28.2.10, 1.3.1, 1.3.2, 1.3.3, 1.3.4, 1.3.5, 1.3.6, 1.3.7, 1.3.8, 1.3.9, 1.3.10, 2.3.1, 2.3.2,
 2.3.3, 2.3.4, 2.3.5, 2.3.6, 2.3.7, 2.3.8, 2.3.9, 2.3.10, 3.3.1, 3.3.2, 3.3.3, 3.3.4, 3.3.5, 3.3.6,
 3.3.7, 3.3.8, 3.3.9, 3.3.10, 4.3.1, 4.3.2, 4.3.3, 4.3.4, 4.3.5, 4.3.6, 4.3.7, 4.3.8, 4.3.9, 4.3.10,
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 30 6.3.5, 6.3.6, 6.3.7, 6.3.8, 6.3.9, 6.3.10, 7.3.1, 7.3.2, 7.3.3, 7.3.4, 7.3.5, 7.3.6, 7.3.7, 7.3.8,
 7.3.9, 7.3.10, 8.3.1, 8.3.2, 8.3.3, 8.3.4, 8.3.5, 8.3.6, 8.3.7, 8.3.8, 8.3.9, 8.3.10, 9.3.1, 9.3.2,
 9.3.3, 9.3.4, 9.3.5, 9.3.6, 9.3.7, 9.3.8, 9.3.9, 9.3.10, 10.3.1, 10.3.2, 10.3.3, 10.3.4, 10.3.5,
 10.3.6, 10.3.7, 10.3.8, 10.3.9, 10.3.10, 11.3.1, 11.3.2, 11.3.3, 11.3.4, 11.3.5, 11.3.6,
 11.3.7, 11.3.8, 11.3.9, 11.3.10, 12.3.1, 12.3.2, 12.3.3, 12.3.4, 12.3.5, 12.3.6, 12.3.7,
 35 12.3.8, 12.3.9, 12.3.10, 13.3.1, 13.3.2, 13.3.3, 13.3.4, 13.3.5, 13.3.6, 13.3.7, 13.3.8,

13.3.9, 13.3.10, 14.3.1, 14.3.2, 14.3.3, 14.3.4, 14.3.5, 14.3.6, 14.3.7, 14.3.8, 14.3.9,
 14.3.10, 15.3.1, 15.3.2, 15.3.3, 15.3.4, 15.3.5, 15.3.6, 15.3.7, 15.3.8, 15.3.9, 15.3.10,
 16.3.1, 16.3.2, 16.3.3, 16.3.4, 16.3.5, 16.3.6, 16.3.7, 16.3.8, 16.3.9, 16.3.10, 17.3.1,
 5 17.3.2, 17.3.3, 17.3.4, 17.3.5, 17.3.6, 17.3.7, 17.3.8, 17.3.9, 17.3.10, 18.3.1, 18.3.2,
 18.3.3, 18.3.4, 18.3.5, 18.3.6, 18.3.7, 18.3.8, 18.3.9, 18.3.10, 19.3.1, 19.3.2, 19.3.3,
 19.3.4, 19.3.5, 19.3.6, 19.3.7, 19.3.8, 19.3.9, 19.3.10, 20.3.1, 20.3.2, 20.3.3, 20.3.4,
 20.3.5, 20.3.6, 20.3.7, 20.3.8, 20.3.9, 20.3.10, 21.3.1, 21.3.2, 21.3.3, 21.3.4, 21.3.5,
 21.3.6, 21.3.7, 21.3.8, 21.3.9, 21.3.10, 22.3.1, 22.3.2, 22.3.3, 22.3.4, 22.3.5, 22.3.6,
 10 22.3.7, 22.3.8, 22.3.9, 22.3.10, 23.3.1, 23.3.2, 23.3.3, 23.3.4, 23.3.5, 23.3.6, 23.3.7,
 23.3.8, 23.3.9, 23.3.10, 24.3.1, 24.3.2, 24.3.3, 24.3.4, 24.3.5, 24.3.6, 24.3.7, 24.3.8,
 24.3.9, 24.3.10, 25.3.1, 25.3.2, 25.3.3, 25.3.4, 25.3.5, 25.3.6, 25.3.7, 25.3.8, 25.3.9,
 25.3.10, 26.3.1, 26.3.2, 26.3.3, 26.3.4, 26.3.5, 26.3.6, 26.3.7, 26.3.8, 26.3.9, 26.3.10,
 27.3.1, 27.3.2, 27.3.3, 27.3.4, 27.3.5, 27.3.6, 27.3.7, 27.3.8, 27.3.9, 27.3.10, 28.3.1,
 15 28.3.2, 28.3.3, 28.3.4, 28.3.5, 28.3.6, 28.3.7, 28.3.8, 28.3.9 and 28.3.10.

Table 4 lists a group of cyclic nucleotide analogs of structure I wherein a heterocyclic ring comprising L^1 and the phosphorus atom of the phosphonate group along with part of the Z-B substructure $-O-CH_2-C^{\#}H(CH_2-)-CH_2-B$. The
 20 unbonded O atom in the Z substructure is linked to L^1 through the α carboxyl group of the amino acid while the CH_2 moiety on the right side is linked to the P atom and the CH_2 moiety linked to the chiral carbon is linked to B (i.e., $-L^1-O-CH_2-C^{\#}H(CH_2-B)-O-CH_2-P(O)(L^2)-$ with $-P(O)(L^2)-$ and $-L^1-$ linked together). Hydrolysis of the compound results in formation of an HPMP
 25 nucleoside phosphonate. A related group of compounds comprises a heterocyclic ring linked through a side chain or other carboxyl group instead of through the carboxyl group linked to the α carbon atom. Hydrolysis of these compounds also result in formation of an HPMP nucleoside phosphonate.

TABLE 4

$L^1-Z(B)-P(O)(L^2)$

- 1 $-NH-CH_2-C(O)-O-CH_2-C^{\#}H(CH_2-B)-O-CH_2-P(O)(L^2)-$
 35 2 $-NH-CH(CH_3)-C(O)-O-CH_2-C^{\#}H(CH_2-B)-O-CH_2-P(O)(L^2)-$
 3 $-NH-CH(CH_3)_2-C(O)-O-CH_2-C^{\#}H(CH_2-B)-O-CH_2-P(O)(L^2)-$

- 4 -NH-CH(CH(CH₃)₂)-C(O)-O-CH₂-C[#]H(CH₂-B)-O-CH₂-P(O)(L²)-
- 5 -NH-CH(CH₃)(CH₃)₂-C(O)-O-CH₂-C[#]H(CH₂-B)-O-CH₂-P(O)(L²)-
- 6 -NH-CH₂-CH₂-CH₂-CH-C(O)-O-CH₂-C[#]H(CH₂-B)-O-CH₂-P(O)(L²)-
- 7 -NH-CH(CH₂-C₆H₅)-C(O)-O-CH₂-C[#]H(CH₂-B)-O-CH₂-P(O)(L²)-
- 5 8 -NH-CH(CH₂-C₈NH₆)-C(O)-O-CH₂-C[#]H(CH₂-B)-O-CH₂-P(O)(L²)-
- 9 -NH-CH(CH₂-CH₂-S-CH₃)-C(O)-O-CH₂-C[#]H(CH₂-B)-O-CH₂-P(O)(L²)-
- 10 -NH-CH(CH₂OH)-C(O)-O-CH₂-O-CH₂-C[#]H(CH₂-B)-O-CH₂-P(O)(L²)-
- 11 -NH-CH(CH(OH)(CH₃))-C(O)-O-CH₂-C[#]H(CH₂-B)-O-CH₂-P(O)(L²)-
- 12 -NH-CH(-CH₂SH)-C(O)-O-CH₂-O-CH₂-C[#]H(CH₂-B)-O-CH₂-P(O)(L²)-
- 10 13 -NH-CH(CH₂-C₆H₅OH)-C(O)-O-CH₂-C[#]H(CH₂-B)-O-CH₂-P(O)(L²)-
- 14 -NH-CH(CH₂-C(O)-NH₂)-C(O)-O-CH₂-C[#]H(CH₂-B)-O-CH₂-P(O)(L²)-
- 15 -NH-CH(CH₂-CH₂-C(O)-NH₂)-C(O)-O-CH₂-C[#]H(CH₂-B)-O-CH₂-P(O)(L²)-
- 16 -NH-CH(CH₂C(O)OR⁴)-C(O)-O-CH₂-C[#]H(CH₂-B)-O-CH₂-P(O)(L²)-
- 17 -NH-CH(CH₂CH₂C(O)OR⁴)-C(O)-O-CH₂-C[#]H(CH₂-B)-O-CH₂-P(O)(L²)-
- 15 18 -NH-CH(CH₂CH₂CH₂CH₂NH₂)-C(O)-O-CH₂-C[#]H(CH₂-B)-O-CH₂-P(O)(L²)-
- 19 -NH-CH(CH₂CH₂CH₂NHC(NH)(NH₂))-C(O)-O-CH₂-C[#]H(CH₂-B)-O-CH₂-P(O)(L²)-
- 20 20 -NH-CH(CH₂C₃N₂H₃)-C(O)-O-CH₂-C[#]H(CH₂-B)-O-CH₂-P(O)(L²)-
- 21 -NH-CH(CH₃)-CH₂-C(O)-O-CH₂-C[#]H(CH₂-B)-O-CH₂-P(O)(L²)-
- 20 22 -NH-CH(CH₂CH₂CH₂NH₂)-CH₂-C(O)-O-CH₂-C[#]H(CH₂-B)-O-CH₂-P(O)(L²)-

L²

- 1 -NH-CH₂-C(O)-OR⁴
- 2 -NH-CH(CH₃)-C(O)-OR⁴
- 25 3 -O-CH₂-O-C(O)-C(CH₃)₃
- 4 -O-CH₂C₆H₅
- 5 -O-C₆H₅
- 6 -O-CH(CH₃)₂
- 7 -NH-CH(CH₂C₆H₄)-C(O)-OR⁴
- 30 8 -OH

B

1. adenin-9-yl
2. guanin-9-yl
- 35 3. cytosin-1-yl

- | | | |
|----|------------------------|------------------------------|
| 4. | 2, 6-diaminopurin-9-yl | |
| 5. | 2-aminopurin-9-yl | 8. 3-deazaadenin-9-yl |
| 6. | 6-azacytosin-1-yl | 9. 8-azaadenin-9-yl |
| 5 | 7. 1-deazaadenin-9-yl | 10. 7-deaza-8-azaadenin-9-yl |
-

* - See Table 1 footnote; the terminal nitrogen and phosphorus atoms are linked to each other.

Compounds listed in Table 4 are designated herein by numbers assigned to L¹, L², and B according to the following convention, L¹.L².B. All Z correspond to the esterified HPMP substructure moiety. Thus, compounds 1.1.3 and 2.4.3 represent compounds designated "glycyl cyclic glycinyl HPMP" and "benzyl cyclic alanyl HPMP" esters. Exemplary compounds include

1.1.1, 1.1.2, 1.1.3, 1.1.4, 1.1.5, 1.1.6, 1.1.7, 1.1.8, 1.1.9, 1.1.10, 2.1.1, 2.1.2, 2.1.3, 2.1.4, 2.1.5, 2.1.6, 2.1.7, 2.1.8, 2.1.9, 2.1.10, 3.1.1, 3.1.2, 3.1.3, 3.1.4, 3.1.5, 3.1.6, 3.1.7, 3.1.8, 3.1.9, 3.1.10, 4.1.1, 4.1.2, 4.1.3, 4.1.4, 4.1.5, 4.1.6, 4.1.7, 4.1.8, 4.1.9, 4.1.10, 5.1.1, 5.1.2, 5.1.3, 5.1.4, 5.1.5, 5.1.6, 5.1.7, 5.1.8, 5.1.9, 5.1.10, 6.1.1, 6.1.2, 6.1.3, 6.1.4, 6.1.5, 6.1.6, 6.1.7, 6.1.8, 6.1.9, 6.1.10, 7.1.1, 7.1.2, 7.1.3, 7.1.4, 7.1.5, 7.1.6, 7.1.7, 7.1.8, 7.1.9, 7.1.10, 8.1.1, 8.1.2, 8.1.3, 8.1.4, 8.1.5, 8.1.6, 8.1.7, 8.1.8, 8.1.9, 8.1.10, 9.1.1, 9.1.2, 9.1.3, 9.1.4, 9.1.5, 9.1.6, 9.1.7, 9.1.8, 9.1.9, 9.1.10, 10.1.1, 10.1.2, 10.1.3, 10.1.4, 10.1.5, 10.1.6, 10.1.7, 10.1.8, 10.1.9, 10.1.10, 11.1.1, 11.1.2, 11.1.3, 11.1.4, 11.1.5, 11.1.6, 11.1.7, 11.1.8, 11.1.9, 11.1.10, 12.1.1, 12.1.2, 12.1.3, 12.1.4, 12.1.5, 12.1.6, 12.1.7, 12.1.8, 12.1.9, 12.1.10, 13.1.1, 13.1.2, 13.1.3, 13.1.4, 13.1.5, 13.1.6, 13.1.7, 13.1.8, 13.1.9, 13.1.10, 14.1.1, 14.1.2, 14.1.3, 14.1.4, 14.1.5, 14.1.6, 14.1.7, 14.1.8, 14.1.9, 14.1.10, 15.1.1, 15.1.2, 15.1.3, 15.1.4, 15.1.5, 15.1.6, 15.1.7, 15.1.8, 15.1.9, 15.1.10, 16.1.1, 16.1.2, 16.1.3, 16.1.4, 16.1.5, 16.1.6, 16.1.7, 16.1.8, 16.1.9, 16.1.10, 17.1.1, 17.1.2, 17.1.3, 17.1.4, 17.1.5, 17.1.6, 17.1.7, 17.1.8, 17.1.9, 17.1.10, 18.1.1, 18.1.2, 18.1.3, 18.1.4, 18.1.5, 18.1.6, 18.1.7, 18.1.8, 18.1.9, 18.1.10, 19.1.1, 19.1.2, 19.1.3, 19.1.4, 19.1.5, 19.1.6, 19.1.7, 19.1.8, 19.1.9, 19.1.10, 20.1.1, 20.1.2, 20.1.3, 20.1.4, 20.1.5, 20.1.6, 20.1.7, 20.1.8, 20.1.9, 20.1.10, 21.1.1, 21.1.2, 21.1.3, 21.1.4, 21.1.5, 21.1.6, 21.1.7, 21.1.8, 21.1.9, 21.1.10, 22.1.1, 22.1.2, 22.1.3, 22.1.4, 22.1.5, 22.1.6, 22.1.7, 22.1.8, 22.1.9, 22.1.10, 1.2.1, 1.2.2, 1.2.3, 1.2.4, 1.2.5, 1.2.6, 1.2.7, 1.2.8, 1.2.9, 1.2.10, 2.2.1, 2.2.2, 2.2.3, 2.2.4, 2.2.5, 2.2.6, 2.2.7, 2.2.8, 2.2.9, 2.2.10, 3.2.1, 3.2.2, 3.2.3, 3.2.4, 3.2.5, 3.2.6, 3.2.7, 3.2.8, 3.2.9, 3.2.10, 4.2.1, 4.2.2, 4.2.3, 4.2.4, 4.2.5, 4.2.6, 4.2.7, 4.2.8, 4.2.9, 4.2.10, 5.2.1, 5.2.2, 5.2.3, 5.2.4, 5.2.5, 5.2.6, 5.2.7, 5.2.8, 5.2.9, 5.2.10, 6.2.1, 6.2.2, 6.2.3, 6.2.4, 6.2.5, 6.2.6, 6.2.7, 6.2.8, 6.2.9, 6.2.10, 7.2.1, 7.2.2, 7.2.3, 7.2.4, 7.2.5, 7.2.6,

7.2.7, 7.2.8, 7.2.9, 7.2.10, 8.2.1, 8.2.2, 8.2.3, 8.2.4, 8.2.5, 8.2.6, 8.2.7, 8.2.8, 8.2.9, 8.2.10,
 9.2.1, 9.2.2, 9.2.3, 9.2.4, 9.2.5, 9.2.6, 9.2.7, 9.2.8, 9.2.9, 9.2.10, 10.2.1, 10.2.2, 10.2.3,
 10.2.4, 10.2.5, 10.2.6, 10.2.7, 10.2.8, 10.2.9, 10.2.10, 11.2.1, 11.2.2, 11.2.3, 11.2.4,
 11.2.5, 11.2.6, 11.2.7, 11.2.8, 11.2.9, 11.2.10, 12.2.1, 12.2.2, 12.2.3, 12.2.4, 12.2.5,
 5 12.2.6, 12.2.7, 12.2.8, 12.2.9, 12.2.10, 13.2.1, 13.2.2, 13.2.3, 13.2.4, 13.2.5, 13.2.6,
 13.2.7, 13.2.8, 13.2.9, 13.2.10, 14.2.1, 14.2.2, 14.2.3, 14.2.4, 14.2.5, 14.2.6, 14.2.7,
 14.2.8, 14.2.9, 14.2.10, 15.2.1, 15.2.2, 15.2.3, 15.2.4, 15.2.5, 15.2.6, 15.2.7, 15.2.8,
 15.2.9, 15.2.10, 16.2.1, 16.2.2, 16.2.3, 16.2.4, 16.2.5, 16.2.6, 16.2.7, 16.2.8, 16.2.9,
 16.2.10, 17.2.1, 17.2.2, 17.2.3, 17.2.4, 17.2.5, 17.2.6, 17.2.7, 17.2.8, 17.2.9, 17.2.10,
 10 18.2.1, 18.2.2, 18.2.3, 18.2.4, 18.2.5, 18.2.6, 18.2.7, 18.2.8, 18.2.9, 18.2.10, 19.2.1,
 19.2.2, 19.2.3, 19.2.4, 19.2.5, 19.2.6, 19.2.7, 19.2.8, 19.2.9, 19.2.10, 20.2.1, 20.2.2,
 20.2.3, 20.2.4, 20.2.5, 20.2.6, 20.2.7, 20.2.8, 20.2.9, 20.2.10, 21.2.1, 21.2.2, 21.2.3,
 21.2.4, 21.2.5, 21.2.6, 21.2.7, 21.2.8, 21.2.9, 21.2.10, 22.2.1, 22.2.2, 22.2.3, 22.2.4,
 22.2.5, 22.2.6, 22.2.7, 22.2.8, 22.2.9, 22.2.10, 1.3.1, 1.3.2, 1.3.3, 1.3.4, 1.3.5, 1.3.6, 1.3.7,
 15 1.3.8, 1.3.9, 1.3.10, 2.3.1, 2.3.2, 2.3.3, 2.3.4, 2.3.5, 2.3.6, 2.3.7, 2.3.8, 2.3.9, 2.3.10, 3.3.1,
 3.3.2, 3.3.3, 3.3.4, 3.3.5, 3.3.6, 3.3.7, 3.3.8, 3.3.9, 3.3.10, 4.3.1, 4.3.2, 4.3.3, 4.3.4, 4.3.5,
 4.3.6, 4.3.7, 4.3.8, 4.3.9, 4.3.10, 5.3.1, 5.3.2, 5.3.3, 5.3.4, 5.3.5, 5.3.6, 5.3.7, 5.3.8, 5.3.9,
 5.3.10, 6.3.1, 6.3.2, 6.3.3, 6.3.4, 6.3.5, 6.3.6, 6.3.7, 6.3.8, 6.3.9, 6.3.10, 7.3.1, 7.3.2, 7.3.3,
 7.3.4, 7.3.5, 7.3.6, 7.3.7, 7.3.8, 7.3.9, 7.3.10, 8.3.1, 8.3.2, 8.3.3, 8.3.4, 8.3.5, 8.3.6, 8.3.7,
 20 8.3.8, 8.3.9, 8.3.10, 9.3.1, 9.3.2, 9.3.3, 9.3.4, 9.3.5, 9.3.6, 9.3.7, 9.3.8, 9.3.9, 9.3.10,
 10.3.1, 10.3.2, 10.3.3, 10.3.4, 10.3.5, 10.3.6, 10.3.7, 10.3.8, 10.3.9, 10.3.10, 11.3.1,
 11.3.2, 11.3.3, 11.3.4, 11.3.5, 11.3.6, 11.3.7, 11.3.8, 11.3.9, 11.3.10, 12.3.1, 12.3.2,
 12.3.3, 12.3.4, 12.3.5, 12.3.6, 12.3.7, 12.3.8, 12.3.9, 12.3.10, 13.3.1, 13.3.2, 13.3.3,
 13.3.4, 13.3.5, 13.3.6, 13.3.7, 13.3.8, 13.3.9, 13.3.10, 14.3.1, 14.3.2, 14.3.3, 14.3.4,
 25 14.3.5, 14.3.6, 14.3.7, 14.3.8, 14.3.9, 14.3.10, 15.3.1, 15.3.2, 15.3.3, 15.3.4, 15.3.5,
 15.3.6, 15.3.7, 15.3.8, 15.3.9, 15.3.10, 16.3.1, 16.3.2, 16.3.3, 16.3.4, 16.3.5, 16.3.6,
 16.3.7, 16.3.8, 16.3.9, 16.3.10, 17.3.1, 17.3.2, 17.3.3, 17.3.4, 17.3.5, 17.3.6, 17.3.7,
 17.3.8, 17.3.9, 17.3.10, 18.3.1, 18.3.2, 18.3.3, 18.3.4, 18.3.5, 18.3.6, 18.3.7, 18.3.8,
 18.3.9, 18.3.10, 19.3.1, 19.3.2, 19.3.3, 19.3.4, 19.3.5, 19.3.6, 19.3.7, 19.3.8, 19.3.9,
 30 19.3.10, 20.3.1, 20.3.2, 20.3.3, 20.3.4, 20.3.5, 20.3.6, 20.3.7, 20.3.8, 20.3.9, 20.3.10,
 21.3.1, 21.3.2, 21.3.3, 21.3.4, 21.3.5, 21.3.6, 21.3.7, 21.3.8, 21.3.9, 21.3.10, 22.3.1,
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Identification of Active Precursors. It is desirable to select the amino acid residue or sequence of the invention compounds having one or more peptide bonds, such as formula VII compounds, based on the substrate specificity of esterases and/or carboxypeptidases expected to be found within cells where precursor hydrolysis is desired. To the extent that the specificity of these enzymes is unknown, one will screen a plurality of nucleotide analogs or esters until the desired substrate specificity is found. This will be apparent from assay either of the generation of free phosphonate or of antimicrobial activity. One selects compounds that are (i) not hydrolyzed or hydrolyzed comparatively slowly in the upper gut, (ii) gut and cell permeable and (iii) hydrolyzed in the cell cytoplasm and/or systemic circulation. Screens with cells from particular tissues are used to identify precursors that are released in organs susceptible to a target viral or microbial infection, e.g. in the case of liver, precursor drugs capable of hydrolysis in the liver. Other infections, e.g.

CMV or HIV, are treated with a precursor that is hydrolyzed at substantially the same rate and to substantially the same degree in all tissues, with no one tissue preferentially hydrolyzing the precursor nucleosides.

The assays used can be those known in the art including intestinal lumen stability, cell permeation, liver homogenate stability and plasma stability assays. These assays are used to determine the bioavailability characteristics of particular active precursors according to routinely used methods.

Therapeutic Indications. The hydrolysis products of the invention compounds have activity against viruses, malignant cells and/or parasitic protozoans. For example, 9-(3-hydroxy-2-phosphonylmethoxypropyl) (HPMP) and (2-phosphonylmethoxy)ethyl (PME) analogs of purine (adenine (A), guanine (G), 2,6-diaminopurine (DAP), 2-monoaminopurine (MAP), hypoxanthine (Hx) and pyrimidine (cytosine (C), uracil (U), thymine (T) were evaluated for antiviral properties. (S)-HPMPA, (S)-cyclic HPMPA, (S)-HPMPC, (S)-HPMPG, (S)-HPMPDAP, PMEDAP, PMEG and PMEA were active against herpes simplex virus, type 1 and 2 (HSV-1 and -2). (S)-HPMPA and (S)-cyclic HPMPA were active against varicella zoster virus (VZV). (S)-HPMPC was active against human cytomegalovirus (HCMV). (S)-HPMPA and (S)-cyclic HPMPA were shown to be active against adenovirus and vaccinia virus. PMEA, PMEDAP, and PMEMAP are active against human immunodeficiency virus (HIV).

Acyclic nucleotide analogs having a common PME side chain covalently linked to a purine or pyrimidine heterocyclic base were prepared and tested for in vivo antiviral activity against retroviruses and herpes viruses. The adenine analog, PMEA, was active in vitro against HIV and Rauscher murine leukemia virus (R-MuLV), and was more potent in vivo than 3'-azido-3'-deoxythymidine (AZT) in the treatment of R-MuLV in mice. PMEA also had a significant antiviral effect in vivo against murine cytomegalovirus (MCMV), and in vitro activity against HCMV. The guanine analog, PMEG, was active in vitro against herpes viruses. In vivo, PMEG was >50-fold more potent than acyclovir against HSV 1 infection in mice.

(S)-HPMPA has potent and selective activity against a broad spectrum of DNA viruses, including HSV-1 and 2, VZV, thymidine kinase-deficient (TK⁻) mutants of herpes simplex virus, HCMV, phocid herpesvirus type 1

(seal herpesvirus, SeHV), simian herpesvirus type 1 (SHV-1), or pseudorabies virus or Aujeszky's disease virus), bovid herpesvirus type 1 (infectious bovine rhinotracheitis virus, BHV-1), equid herpesvirus type 1 (equine abortion virus, EHV-1), African swine fever (ASF) virus, vaccinia virus; and
5 human adenoviruses, and retroviruses such as murine sarcoma virus (MSV). It is also reported that, in mice and rabbits in vivo, the compound is effective against both local and systemic infections with herpes simplex virus type 1, including herpetic keratitis caused by a TK⁻ mutant which is resistant to the classical antiherpes drugs (DeClercq, E., et al, Antiviral Res (1987) 8:261-272;
10 DeClercq, E., et al, Nature (1986) 323:464-467; Gil-Fernandez, C., et al, Antiviral Res (1987) 7:151-160; Baba, M., et al, Antimicrob Agents Chemother (1987) 31:337-339).

Phosphonylmethoxyalkylpurine analogs have also been evaluated for their antitumor activity in murine tumor models. HPMPA, PMEA, and
15 PMEG were found to be active against intraperitoneal P388 leukemia. PMEG was also found to be active against B16 melanoma.

As indicated above, the compounds of the invention are useful for treatment of microbial infections, for treatment of tumors or for other indications described below. Microbial infections include infection by viruses,
20 parasites, yeasts and fungi. Exemplary viral infections that may be treated include infections mediated by DNA or RNA viruses including herpesviruses (CMV, HSV 1, HSV 2, EBV, varicella zoster virus, bovid herpesvirus type 1, equid herpesvirus type 1), papillomaviruses (HPV types 1-55), flaviviruses (including African swine fever virus and Japanese
25 encephalitis virus), togaviruses (including Venezuelan equine encephalomyelitis virus), influenza viruses (types A-C), retroviruses (HIV 1, HIV 2, HTLV I, HTLV II, SIV, HBV, FeLV, FIV, MoMSV), adenoviruses (types 1-8), poxviruses (vaccinia virus), enteroviruses (polio virus type 1-3, hepatitis A virus), gastroenteritis viruses (Norwalk viruses, rotaviruses), hantaviruses
30 (Hantaan virus), papovaviruses, rhinoviruses, parainfluenza virus types 1-4, rabies virus, and the like.

Some of the phosphonate compounds (such as PMEA) have a broad spectrum of antimicrobial activity and are thus unusual antiviral or antiparasitic agents. The activity of individual nucleotide analogs and
35 nucleotide analog amidates is determined by routine assay of antiviral (or

other antimicrobial) activity using enzyme inhibition assays, tissue culture assays, animal model assays and/or other acceptable assays.

Nucleotide analogs (phosphonates such as HPMPC, PMEA, etc) are believed to exert their antimicrobial activity, at least in part, by a two step enzyme-mediated conversion to a diphosphate, followed by incorporation of the diphosphorylated nucleotide analog into nucleic acids. The incorporation of the diphosphates into nucleic acid is mediated by viral or other microbial DNA or RNA polymerases (bacterial, retroviral, etc). Thus, nucleotide analogs (when diphosphorylated) are useful as chain terminators for dideoxynucleotide-type DNA sequencing protocols, provided that the nucleotide analog lacks a free hydroxyl group suitable for polymerase mediated chain elongation. These compounds will not have a hydroxyl group at R²⁷ in compounds of formulas IV and VI or are acyclic. Nucleotide analogs of formula XV, (HO)₂P(O)-O-P(O)(OH)-O-(HO)P(O)-Z-B, can be prepared (Otvos, et al, Nucl Acids Res (1987) 15:1763-1777) and provided in a kit with other reagents (such as klenow polymerase or T4 polymerase, dNTPs, etc) needed for DNA sequencing. The invention nucleotide analogs and nucleotide analog amidates can also be (1) applied to tissue culture systems to eliminate or reduce viral spread or growth during the production of biopharmaceuticals or other products (such as proteins or vaccines), (2) used to eliminate or reduce viral spread or growth in clinical samples (such as blood), and (3) used to stop growth of tissue culture or bacterial cells (using toxic amounts of compound) without interfering with protein production.

Infections mediated by protozoan parasites can be treated using the compounds of the invention. Such infections can also be treated using the corresponding nucleotide analogs of the invention nucleotide analog amidates. The term protozoa is intended to include those members of the subphyla *Sarcomastigophora* and *Sporozoa* of the phylum *Protozoa*. More particularly, the term protozoa as used herein is intended to include those genera of parasitic protozoa which are important to man because they either cause disease in man or in his domestic animals. These genera are for the most part found classified in the superclass *Mastigophora* of the subphylum *Sarcomastigophora* and the class *Telosporea* of the subphylum *Sporozoa* in the classification according to Baker (1969). Illustrative genera of these parasitic protozoa include *Histomonas*, *Pneumocystis*, *Trypanosoma*, *Giardia*,

Trichomonas, *Eimeria*, *Isopora*, *Leishmania*, *Entamoeba*, *Toxoplasma* and *Plasmodium*. Parasitic protozoans include *Plasmodium falciparum*, *Plasmodium berghei*, *Plasmodium malariae*, *Plasmodium vivax*, *Leishmania braziliensis*, *Leishmania donovani*, *Trypanosoma cruzi*, *Trypanosoma brucei*,
5 *Trypanosoma rhodesiense*, *Pneumocystis carinii*, *Entamoeba histolytica*, *Trichomonas vaginalis* and the like (de Vries, E., et al, Mol Biochem Parasitol (1991) 47:43-50). Nucleoside analog amidates of the invention and/or their corresponding nucleotide analogs can also be used to treat yeast or fungal infections caused by *Candida glabrata*, *Candida tropicalis*, *Candida albicans*,
10 and other *Candida* species *Cryptococcus* species including *Cryptococcus neoformans*, *Blastomyces* species including *Blastomyces dermatidis*, *Torulopsis* species including *Torulopsis glabrata*, *Coccidioides* species including *Coccidioides immitis*, *Aspergillus* species and the like.

15 Pharmaceutical formulations. Compounds of the invention and their physiologically acceptable salts (hereafter collectively referred to as the active ingredients) may be administered by any route appropriate to the condition to be treated, suitable routes including oral, rectal, nasal, topical (including ocular, buccal and sublingual), vaginal and parenteral (including
20 subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural). The preferred route of administration may vary with for example the condition of the recipient.

While it is possible for the active ingredients to be administered alone it is preferably to present them as pharmaceutical formulations. The
25 formulations, both for veterinary and for human use, of the present invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious
30 to the recipient thereof.

The formulations include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural) administration. The formulations may conveniently be presented
35 in unit dosage form and may be prepared by any of the methods well known

in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with
5 liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or
10 granules; as solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with
15 one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the
20 powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

For infections of the eye or other external tissues e.g. mouth and skin, the formulations are preferably applied as a topical ointment or cream
25 containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or
30 a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol,
35 sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures

thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

5 The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included
10 together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

15 Emulgents and emulsion stabilizers suitable for use in the formulation of the present invention include Tween[®] 60, Span[®] 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

 The choice of suitable oils or fats for the formulation is based on
20 achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic
25 alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required.
30 Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

 Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The
35 active ingredient is preferably present in such formulations in a

concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose
5 and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a
10 salicylate.

Formulations suitable for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns (including particle sizes in a range between 20 and 500 microns in increments of 5 microns such as 30 microns, 35 microns, etc),
15 which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as for example a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol
20 administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as pentamidine for treatment of pneumocystis pneumonia.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations
25 containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with
30 the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier,
35 for example water for injections, immediately prior to use. Extemporaneous

injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of an active
5 ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include
10 flavoring agents.

The present invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

Veterinary carriers are materials useful for the purpose of
15 administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

Compounds of the invention can be used to provide controlled release
20 pharmaceutical formulations containing as active ingredient one or more compounds of the invention ("controlled release formulations") in which the release of the active ingredient can be controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given invention compound. Controlled release formulations adapted for
25 oral administration in which discrete units comprising one or more compounds of the invention can be prepared according to conventional methods. Controlled release formulations may be employed for the treatment or prophylaxis of various microbial infections particularly human bacterial, human parasitic protozoan or human viral infections caused by
30 microbial species including *Plasmodium*, *Pneumocystis*, herpesviruses (CMV, HSV 1, HSV 2, VZV, and the like), retroviruses, adenoviruses and the like. The controlled release formulations can be used to treat HIV infections and related conditions such as tuberculosis, malaria, pneumocystis pneumonia, CMV retinitis, AIDS, AIDS-related complex (ARC) and
35 progressive generalized lymphadeopathy (PGL), and AIDS-related

neurological conditions such as multiple sclerosis, and tropical spastic paraparesis. Other human retroviral infections that may be treated with the controlled release formulations according to the invention include Human T-cell Lymphotropic virus (HTLV)-I and IV and HIV-2 infections.

5 The invention accordingly provides pharmaceutical formulations for use in the treatment or prophylaxis of the above-mentioned human or veterinary conditions and microbial infections.

Therapeutic Administration. For each of the above-indicated utilities
10 and indications the amount required of an active ingredient (as above defined) will depend upon a number of factors including the severity of the condition to be treated and the identity of the recipient and will ultimately be at the discretion of the attendant physician or veterinarian. In general
15 however, for each of these utilities and indications, a suitable, effective dose will be in the range 0.1 to 250 mg per kilogram bodyweight of recipient per dose (including active ingredient(s) in a range between 0.1 mg and 250 mg/Kg/dose in increments of 0.5 mg/Kg/dose such as 2.5 mg/Kg/dose, 3.0 mg/Kg/dose, 3.5 mg/Kg/dose, etc), preferably in the range 0.5 to 50 mg per
20 kilogram body weight per dose and most preferably in the range 1 to 15 mg per kilogram body weight per dose; an optimum dose is about 3.0 mg per kilogram body weight per dose. (Unless otherwise indicated all weights of active ingredient are calculated as the parent compound of formula I: for salts thereof the figures would be increased proportionately). The desired dose is preferably presented as one dose or two sub-doses administered at appropriate
25 intervals throughout a period of one to seven days. It is preferred to administer a dose once every 2, 3, 4, 5 or 6 days. The doses may be administered in unit dosage forms. The desired dose is may be presented as one, two, or three sub-doses administered at appropriate intervals throughout the one to seven day period. These sub-doses may be administered in unit
30 dosage form, for example, containing 10 to 1000 mg, and or 100 to 500 mg of active ingredient per unit dosage form. The formulations should be desirably administered to achieve peak plasma concentrations of the active compound of from about 1 to about 100 μ M, preferably about 2 to 50 μ M, most preferably about 3 to about 30 μ M.

Compounds such as those of structures XXXI, XXXII and XXXIII (defined below) will generally (1) have a higher oral bioavailability than the corresponding uncyclized nucleotide analog (e.g., cHPMPC compared to HPMPC) and/or (2) will exhibit reduced toxicity when compared with the same dose of the corresponding uncyclized nucleotide analog, and/or (3) will have greater efficacy when compared with the same dose of the corresponding uncyclized nucleotide analog.

The compounds of the invention may be employed in combination with other therapeutic agents for the treatment or prophylaxis of the infections or conditions indicated above. Examples of such further therapeutic agents include agents that are effective for the treatment or prophylaxis of viral, parasitic or bacterial infections or associated conditions or for treatment of tumors or related conditions include 3'-azido-3'-deoxythymidine (zidovudine, AZT), 2'-deoxy-3'-thiacytidine (3TC), 2',3'-dideoxy-2',3'-didehydroadenosine (D4A), 2',3'-dideoxy-2',3'-didehydrothymidine (D4T), carbovir (carbocyclic 2',3'-dideoxy-2',3'-didehydroguanosine), 3'-azido-2',3'-dideoxyuridine, 5-fluorothymidine, (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU), 2-chlorodeoxyadenosine, 2-deoxycoformycin, 5-fluorouracil, 5-fluorouridine, 5-fluoro-2'-deoxyuridine, 5-trifluoromethyl-2'-deoxyuridine, 6-azauridine, 5-fluoroorotic acid, methotrexate, triacetyluridine, 1-(2'-deoxy-2'-fluoro-1- β -arabinosyl)-5-iodocytidine (FIAC), tetrahydro-imidazo(4,5,1-jk)-(1,4)-benzodiazepin-2(1H)-thione (TIBO), 2'-nor-cyclicGMP, 6-methoxypurine arabinoside (ara-M), 6-methoxypurine arabinoside 2'-O-valerate, cytosine arabinoside (ara-C), 2',3'-dideoxynucleosides such as 2',3'-dideoxycytidine (ddC), 2',3'-dideoxyadenosine (ddA) and 2',3'-dideoxyinosine (ddI), acyclic nucleosides such as acyclovir, penciclovir, famciclovir, ganciclovir, HPMPC, PMEA, PMEG, PMPA, PMPDAP, FMPA, HPMPA, HPMPDAP, (2R, 5R)-9-[tetrahydro-5-(phosphonomethoxy)-2-furanyl]adenine, (2R, 5R)-1-[tetrahydro-5-(phosphonomethoxy)-2-furanyl]thymine, other antivirals including ribavirin (adenine arabinoside), 2-thio-6-azauridine, tubercidin, aurintricarboxylic acid, 3-deazaneoplanocin, neoplanocin, rimantidine, adamantane, and foscarnet (trisodium phosphonoformate), antibacterial agents including bactericidal fluoroquinolones (ciprofloxacin, pefloxacin and the like), aminoglycoside bactericidal antibiotics (streptomycin, gentamicin,

amicacin and the like) β -lactamase inhibitors (cephalosporins, penicillins and the like), other antibacterials including tetracycline, isoniazid, rifampin, cefoperazone, clathromycin and azithromycin, antiparasite or antifungal agents including pentamidine (1,5-bis(4'-aminophenoxy)pentane), 9-
5 deazainosine, sulfamethoxazole, sulfadiazine, quinapyramine, quinine, fluconazole, ketoconazole, itraconazole, Amphotericin B, 5-fluorocytosine, clotrimazole, hexadecylphosphocholine and nystatin, renal excretion inhibitors such as probenecid, nucleoside transport inhibitors such as dipyrindamole, dilazep and nitrobenzylthioinosine, immunomodulators such
10 as FK506, cyclosporin A, thymosin α -1, cytokines including TNF and TGF- β , interferons including IFN- α , IFN- β and IFN- γ , interleukins including interleukin I, II, III, IV, V, VI, VII, VIII, X, XII, XIII macrophage/granulocyte colony stimulating factors including GM-CSF, G-CSF, M-CSF, cytokine antagonists including anti-TNF antibodies, anti-interleukin antibodies,
15 soluble interleukin receptors, protein kinase C inhibitors and the like.

Immunogens and Antibodies. The compounds of this invention, or the biologically active substances produced from these compounds by hydrolysis in vivo, are used as immunogens to prepare antibodies capable of
20 binding specifically to the compounds or their hydrolysis products. The immunogenic compositions therefore are useful as intermediates in the preparation of antibodies for use in diagnostic or quality control assays for the compounds or their hydrolysis products. The antibodies are useful for measuring the presence, absence or amounts of the compounds by any
25 convenient homogenous or heterogenous procedure such as fluorescence polarization immunoassay, fluorescence immunoassay (using fluorescent labels such as fluorescein and the like), radioimmunoassay, enzyme immunoassay (using enzyme indicators such as alkaline phosphatase, horseradish peroxidase, glucose oxidase, urease and the like) and
30 nephelometric inhibition assay by described methods (WO 92/22639, incorporated herein by reference). Such assays usually require a tracer (such as a fluorescent or radiolabeled labeled invention compound), an antibody and the sample to be analyzed containing the compound.

The hydrolysis products of interest are the phosphonates resulting
35 from the hydrolysis of the amidate or ester bond(s) of the precursor

compounds of this invention, for example HPMPC, 6-aza-HPMPC, cyclic HPMPC, PMEA, PMEG, PMPDAP, PMPA, D4TMPI, D4AMPI, cyclic HPMPA, FPMPA, PMEDAP, PMEMAP, 7-deaza-8-aza-FPMPA, 7-deaza-8-aza-HPMPA, cyclic 7-deaza-8-aza-HPMPA, 7-deaza-8-aza-PMPA, 8-aza-FPMPA, 8-aza-HPMPA, cyclic 8-aza-HPMPA, 8-aza-PMPA, PMPG, PMPMAP, 1-deaza-HPMPA, cyclic 1-deaza-HPMPA, 1-deaza-PMPA, 1-deaza-PMPG, 1-deaza-PMPMAP, 1-deaza-PMPDAP, 3-deaza-HPMPA, cyclic 3-deaza-HPMPA or 3-deaza-PMPA. Thus, the antibodies of this invention will be capable of binding to the precursors without binding to the hydrolysis products, will be capable of binding to the hydrolysis products without binding to the precursors, or will be capable of binding specifically to both. The antibodies will not cross-react with naturally-occurring nucleotides or nucleosides.

The immunogens of this invention contain the precursor or hydrolytic products in association with an immunogenic substance such as a protein or peptide. Immunogenic substances include adjuvants such as Freund's adjuvant, immunogenic proteins such as viral, bacterial, yeast, plant and animal polypeptides, in particular keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin or soybean trypsin inhibitor, and immunogenic polysaccharides. Typically, the precursor or a compound having the structure of a precursor hydrolytic product is covalently conjugated to an immunogenic polypeptide or polysaccharide by the use of a polyfunctional (ordinarily bifunctional) cross-linking agent. Methods for the manufacture of haptens are conventional per se, and any of the methods used heretofore for conjugating haptens to immunogenic polypeptides or the like are suitably employed here as well, taking into account the functional groups on the precursors or hydrolytic products which are available for cross-linking.

Typically the polypeptide is conjugated to a site on the heterocyclic base functionality of the compound or hydrolysis product rather than to a site on the alkyl or substituted-alkyl phosphonate moiety. In general, the site will be an amino group located on the purine or pyrimidine moiety of the nucleoside phosphonate, at the 5 position of pyrimidines (such as cytosine or uracil), at the 1 position of purines (such as adenosine or guanine) or, for compounds having a cyclic structure corresponding to a sugar or sugar analog and having a free hydroxyl group, through the hydroxyl group (usually at the

3' or 2' positions). Alternatively, the precursor compound is cross-linked through the phosphonate, typically by amidation or esterification of the phosphonate by the polypeptide itself or by a cross-linking functionality covalently bonded to the polypeptide. Thus, the groups L^1 or L^2 in structures
5 $(L^1)(L^2)-P(O)-Z-B$ can be immunogenic proteins (having more than 50 amino acid residues, usually less than 1000 residues) or peptides (about 5 to 50 amino acid residues).

The conjugates are prepared in conventional fashion. For example, N-hydroxysuccinimide, succinic anhydride or $alkN=C=Nalk$ are useful in
10 preparing the conjugates of this invention. The conjugates contain a precursor, its hydrolysis product, or both. Ordinarily, the conjugates will comprise the hydrolysis product, i.e., the biologically active drug. The conjugates are separated from starting materials and byproducts using chromatography or the like, and then are sterile filtered and vialled for
15 storage.

Animals are typically immunized against the immunogenic conjugates or derivatives by combining 1 mg or 1 μ g of conjugate (for rabbits or mice, respectively) with 3 volumes of Freund's complete adjuvant and injecting the solution intradermally at multiple sites. One month later the animals are
20 boosted with 1/5 to 1/10 the original amount of conjugate in Freund's complete adjuvant (or other suitable adjuvant) by subcutaneous injection at multiple sites. 7 to 14 days later animals are bled and the serum is assayed for the desired antibody titer. Animals are boosted until the titer plateaus. Preferably, the animal is boosted with the conjugate in which the precursor or
25 product is linked to a different protein, through a different cross-linking agent or both. Optionally, aggregating agents such as alum are used to enhance the immune response.

After immunization, monoclonal antibodies are prepared by recovering immune lymphoid cells (typically spleen cells or lymphocytes
30 from lymph node tissue) from immunized animals and immortalizing the cells in conventional fashion, e.g., by fusion with myeloma cells or by Epstein-Barr virus transformation and screening for clones expressing the desired antibody. The hybridoma technique described originally by Kohler and Milstein, Eur. J. Immunol. (1976) 6:511 has been widely applied to

produce hybrid cell lines that secrete high levels of monoclonal antibodies against many specific antigens.

It is possible to fuse cells of one species with another. However, it is preferably that the source of the immunized antibody producing cells and the
5 myeloma be from the same species.

The hybrid cell lines are maintained in culture in vitro. The cell lines of this invention are selected or maintained in a hypoxanthine-aminopterin thymidine (HAT) medium. However, the established hybridoma cell line can be maintained on a variety of nutritionally adequate media. The secreted
10 antibody is recovered from culture by conventional methods such as precipitation, ion exchange chromatography, affinity chromatography, or the like. The antibodies described herein are also recovered from hybridoma cell cultures by conventional methods for purification of IgG or IgM as the case may be that heretofore have been used to purify immunoglobulins from
15 pooled plasma, e.g., ethanol or polyethylene glycol precipitation procedures. The purified antibodies are sterile filtered, and optionally are conjugated to a detectable marker such as an enzyme or spin label for use in diagnostic assays of test samples.

The antibodies of this invention are obtained from any animal species,
20 but ordinarily are murine or rat. Once a monoclonal antibody having the desired specificity and affinity is obtained, other conventional modifications of the antibodies are within the scope of this invention. For example, the complementarity determining regions of an animal antibody, together with as much of the framework domain as is needed, are substituted into an
25 antibody of another animal species or class to produce a cross-class or cross-species chimeric antibody. Fragments or other amino acid sequence variants of monoclonal antibodies also are encompassed within the meaning of antibody as that term is used herein, for example, Fab, Fab' or (Fab')₂ fragments, single chain antibodies, bi or polyspecific antibodies, and the like.

30 The antibodies of this invention are from any suitable class or isotype, e.g. IgG, IgM, IgA, IgD or IgE. They may or may not participate in complement binding or ADCC.

Typically, hybridomas which are capable of binding to the immunogen are screened for the ability to bind to the hapten itself in typical test samples
35 (plasma, serum and the like) with the requisite degree of affinity. The desired

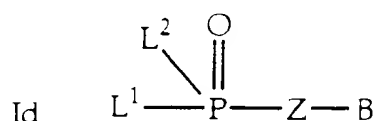
affinity will depend upon the use intended for the antibody, but should be adequate to function in a conventional competitive-type ELISA or radioimmunoassays, or in conventional EMIT immunoassays.

5 The antibodies of this invention are used in such assays together with a labeled form of the precursor or its hydrolytic product. Alternatively, the antibody is labeled. Suitable labels are well-known and include radioisotopes, enzymes, stable free radicals, fluorophors, chemiluminescent moieties and other detectable groups heretofore employed to prepare covalent conjugates
10 for use in assays. Methods for linking the labels to ligand amino groups, or amino acid side chains or termini of polypeptides, are known and are suitable for use herein. Other suitable linking methods will be apparent to the ordinary artisan.

15 The antibodies and labeled ligands herein optionally are assembled into kits for use in therapeutic drug monitoring or evaluation, or for process quality control, and used in the conventional manner.

Diagnostic applications. Novel compounds described herein are useful as intermediates in the preparation of detectable labels for oligonucleotide
20 probes. The compounds are hydrolyzed to the diacid, diphosphorylated and then incorporated into an oligonucleotide by conventional enzymatic or chemical means. The incorporated heterocyclic base from the invention will generally be capable of participating in heterocyclic base pairing and thus will not interfere substantially with the binding of the oligonucleotide to its
25 complementary sequence (E. DeClerq (1993) 3:85-96); should it interfere with oligonucleotide binding to its complementary sequence, the nucleotide analog is incorporated as the final 3' terminal residue, an innocuous position and a conventional site for oligonucleotide labeling. The nucleotide analog compound in the oligonucleotide is detected by any means, such as NMR,
30 immune, fluorescence or radiolabel detection.

Bis amidate synthesis. Synthesis of bis-phosphoroamidate nucleotide analogs of Formula Id,



where L¹ and L² are the same and are an amino acid, dipeptide, tripeptide or oligopeptide (4, 5 or 6 amino acid residues) are prepared by conversion of a nucleotide analog (such as PMEA, HPMPC, HPMPA, PMEG, FMPMA,

- 5 PMPDAP, 9-[2,3-dideoxy-2,3-didehydro-4-phosphonomethoxy-β-D-erythrofuransyl]adenine (D4AMPI; reg no. 132178-53-1), 1-[2,3-dideoxy-2,3-didehydro-4-phosphonomethoxy-β-D-erythrofuransyl]thymine (D4TMPI; reg no. 132178-49-5) and the like) directly to the corresponding bis-phosphoroamidate compound. L¹ is a protein, an amino acid, dipeptide, 10 tripeptide or oligopeptide (4 to 6 amino acid residues) which is esterified at free α-carboxyl group(s) by R⁴. Suitable R⁴ groups include methyl, ethyl, propyl, isopropyl, butyl, t-butyl, phenyl, benzyl, N-ethylmorpholino, pivaloyloxymethyl and the like. The amino acids can comprise an aliphatic or aromatic side group (such as ala, phe, pro, leu, ile, met, trp and the like) or 15 a dipeptide comprising amino acids having aliphatic or aromatic side groups (such as gly-gly, ala-ala, gly-ala, ala-gly, phe-gly, gly-phe, ala-phe, phe-ala, leu-ala, ala-leu and the like), or is a tripeptide comprising amino acids having aliphatic or aromatic side groups or is an oligopeptide comprising amino acids having aliphatic or aromatic side groups.

- 20 The procedure is suitable for all of the nucleotide analogs described herein. The synthesis is accomplished by suspension of the nucleotide analog and approximately 2 equivalents of the L¹ species in a solvent such as dry pyridine or DMF (dimethylformamide) optionally containing a non-nucleophilic organic base such as triethylamine (about 3 to 10 equivalents).
- 25 The dehydration step is accomplished by modification of a described reaction (Mukaiyama, T. et al, J Am Chem Soc (1972) 94:8528-8532) by adding a 1:1 mixture of triphenylphosphine (reg. no. 603-35-0; Aldrich) and 2,2'-dipyridyl disulfide (2 to 4 equivalents; reg. no. 2127-03-9; Aldrich) in pyridine to the nucleotide analog/amino acid mixture and (a) stirring at room temperature 30 for about 4 to 16 hours or (b) heating to 60° C to 100° C (including any temperature in one degree C increments between 60° and 100° C such as 70°, 80° or 90° C) for about 4 to 16 hours. The resulting reaction mixture is then

concentrated and the final bis-amidate product is recovered and purified by conventional methods.

5 An alternative reaction suitable for synthesizing most amidate compounds is converting a nucleotide analog phosphonate to the corresponding chloridate by reaction with thionyl chloride in solvent (DMF) as described in EP 481 214. An amino acid, dipeptide or other molecule bearing a free amine is then reacted with the chloridate to yield the corresponding bis-amidate.

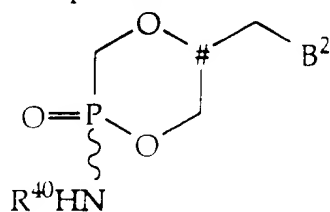
10 Synthesis of compounds of Formula Id having amino acids that contain amino, guanidino or carboxyl groups (such as lys, arg, his, asn, gln, lys-lys, arg-arg, lys-arg and the like) is accomplished by the same method, but using protected amine or carboxyl groups. After synthesis of the protected bis-amidate compound, the protecting groups are removed by conventional methods. Suitable protecting groups are well known and include acid labile groups such as p-tosyl, BOC (t-butoxycarbonyl) and FMOC (fluorene methoxycarbonyl) for protecting amine groups. Groups such as t-butyl, methyl, ethyl, benzyl and the like can be used to protect carboxyl groups. These groups can be removed under acid, base or hydrogenolysis conditions or can be removed with an esterase according to conventional methods.

20 Synthesis of compounds of Formula Id having amino acids such as tyr, cys, ser and thr is accomplished by optionally protecting hydroxyl or thiol groups using protecting groups known in the art. For example, the hydroxyl group of ser, thr or tyr can be protected using benzyl, ethyl and the like and the thiol group of cys can be protected using trityl, p-methylbenzyl and the like. The choice of a protecting group will depend on the stability of the bis-amidate toward conditions used to remove a particular protecting group. Appropriate protecting groups can be selected or determined by the skilled artisan using routine methods.

30 Dipeptide or tripeptide species can be selected on the basis of known transport properties and/or susceptibility to peptidases that can affect transport to intestinal mucosal or other cell types. Dipeptides and tripeptides lacking an α -amino group are transport substrates for the peptide transporter found in brush border membrane of intestinal mucosal cells (Bai, J.P.F., Pharm Res (1992) 9:969-978). Transport competent peptides can thus be used
35 to enhance bioavailability of bis amidate compounds. Di- or tripeptides

having one or more amino acids in the D configuration are also compatible with peptide transport and can be utilized in bis amidate compounds. Amino acids in the D configuration can be used to reduce the susceptibility of a di- or tripeptide to hydrolysis by proteases common to the brush border such as aminopeptidase N (EC 3.4.11.2). In addition, di- or tripeptides with amino acid residues can be selected on the basis of their relative resistance to hydrolysis by proteases found in the lumen of the intestine. For example, tripeptides or oligopeptides lacking asp and/or glu are poor substrates for aminopeptidase A (EC 3.4.11.7) and di- or tripeptides lacking amino acid residues on the N-terminal side of hydrophobic amino acids (leu, tyr, phe, val, trp) are poor substrates for endopeptidase 24.11 (EC 3.4.24.11) while peptides lacking a pro residue at the penultimate position at a free carboxyl terminus are poor substrates for carboxypeptidase P (EC 3.4.17). Similar considerations can also be applied to the selection of peptides that are either relatively resistant or relatively susceptible to hydrolysis by cytosolic, renal, hepatic, serum or other peptidases.

Synthesis of N-alkylamine amidates (where $-NHR^{40}$ is linked to the phosphorus atom and R^{40} is C_{1-20} alkyl, including C_{4-16} alkyl) is accomplished essentially as described (Saito *Chem. Pharm. Bull.* (1991) 39:3207). Thus, compounds such as, for example, of structure $(R^{40}HN)(L^1)P(O)-Z-B^2$ or



wherein B^2 is B or B^1 , are synthesized in this manner.

Amidate-ester synthesis. Synthesis of mixed amidate-ester nucleotide analog amidates of Formula Id where L^1 is an amino acid ester and L^2 is a group of the formula OR, SR or OR^{31} is accomplished by conversion of a nucleotide analog (such as PMEA, HPMPC, HPMPA, PMEG, FMPMPA, PMPDAP, D4AMPI, D4TMPI and the like) di- or bis-ester to a corresponding mixed ester-phosphoroamidate compound. A bis ester is converted to a mono ester by treatment with a base such as ammonia to remove one ester group. The resulting mono ester is then converted to a mixed amidate-ester as described for synthesis of bis amidate compounds.

Bis ester synthesis. Bis esters of the formula $(RO)_2P(O)-Z-B$ are generally synthesized as described in EP 481 214 or as described in Mukaiyama, T. et al, J Am Chem Soc (1972) 94:8528-8532. Dialkyl phosphonate esters are synthesized via conversion of a dichlorophosphonate (chloridate) such as

5 $(Cl)_2P(O)-Z-B$ (Quast, H. et al, Synthesis (1974) Z:489-490; Quast, H. et al, Synthesis (1974) Z:490; Moedritzer, K. et al, Synth Reac Inorg Met - Org Chem (1974) 5:417-27; Moedritzer, K., Chem Abs 82:86340; Stowell, M.H.B., et al Tet Lett (1990) 31:3261-3262) to a corresponding dialkylester (or dialkylamide) by reaction with alcohols (or amines). Monoalkylesters (or mono alkylamides)

10 are obtained by hydrolysis of the disubstituted phosphonate in base (NaOH, KOH and the like). Disubstituted diacyloxyalkyl phosphonates are obtained by reaction of the unsubstituted phosphonate with a substituted chloromethyl ester $(R-C(O)-O-CH(R)-Cl)$. A corresponding monosubstituted acyloxyalkyl phosphonate is obtained by hydrolysis in acid or base.

15 For synthesis of Z substructures having a free hydroxyl group, such as $(RO)_2P(O)-CH_2-O-CH(CH_2OH)-CH_2-$, the hydroxyl is, in some cases, protected by a protecting group such as benzyl, acetyl, trityl, dimethoxytrityl and the like.

Bis esters having aryl, substituted aryl, alkyl-aryl or substituted alkyl-aryl (such as phenyl, alkoxyphenyl, benzyl, alkoxybenzyl) are also synthesized

20 as described by reaction of $(OH)_2P(O)-B-Z$ with thionyl chloride and a catalytic amount of DMF in a solvent such as acetonitrile. The resulting dichloridate, $P(O)(Cl)_2-Z-B$ is then reacted with about 4, 5 or 6 equivalents of the sodium or potassium alkoxide or a sodium or potassium aryloxide obtained from

25 reaction with sodium hydride or potassium hydride and the alcohol (such as phenol, benzyl alcohol and the like) in a solvent such as THF or acetonitrile at a reduced temperature (below about $-70^\circ C$, preferably about $-76^\circ C$ to $-78^\circ C$).

cHPMPC and the cyclic analogues of other cHPMPs are prepared by a number of methods from the free hydroxy phosphonic acid. These methods

30 include treatment with DCC in DMF, reaction with Vilsmeier's reagent $(ClCH=N(CH_3)_2Cl)$, or methods of phosphate activation known per se. In one embodiment of this invention for the preparation of a cHPMP from the corresponding phosphonate nucleotide analog, the phosphonate is (a) treated with $ClCH=N(CH_3)_2Cl$ to yield the phosphonylchloridate and (b) optionally

the phosphonylchloride is reacted with a nucleophile (preferably at low temperature, e.g. lower than about -20°C) such as an alcohol or amine to produce one of the intermediates described above. In a further step the product of steps (a) or (b) are subject to hydrolysis or protonolysis (typically acid protonolysis) respectively to yield the cHSNA (treatment of the product of step (a)) or its intermediate (treatment of the product of step (b)).

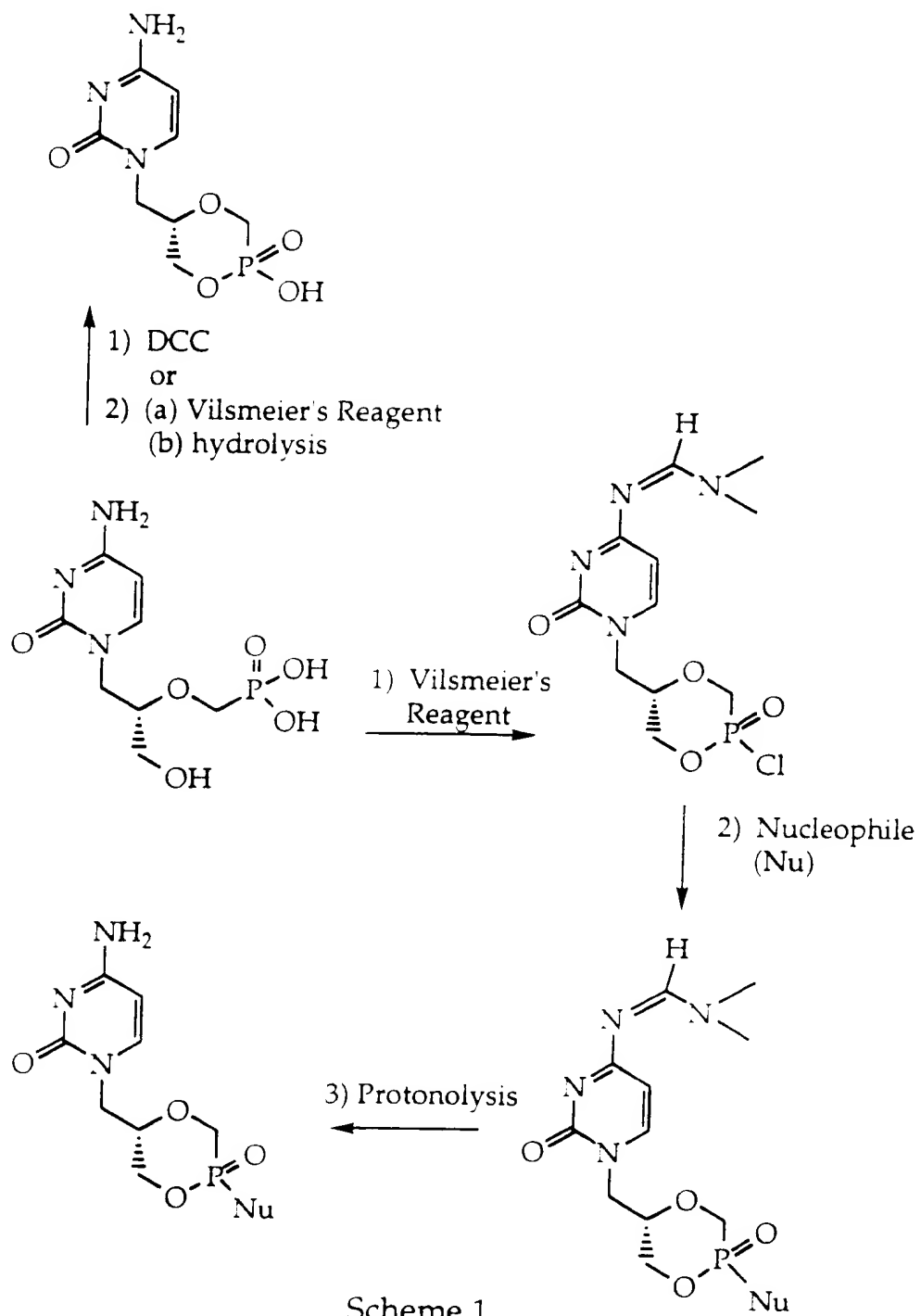
Vilsmeier's reagent is advantageously produced *in situ* by combining SOCl_2 , PCl_5 , POCl_3 , COCl_2 or the like with DMF. Advantageously, the product of step (a) is not purified or separated from the reaction mixture before being reacted with the nucleophile, a distinct economic advantage for this synthetic route. The compounds of structure (Ia) and (Va) are readily made from their uncyclized counterparts by the same methods, e.g. treatment with DCC in DMF.

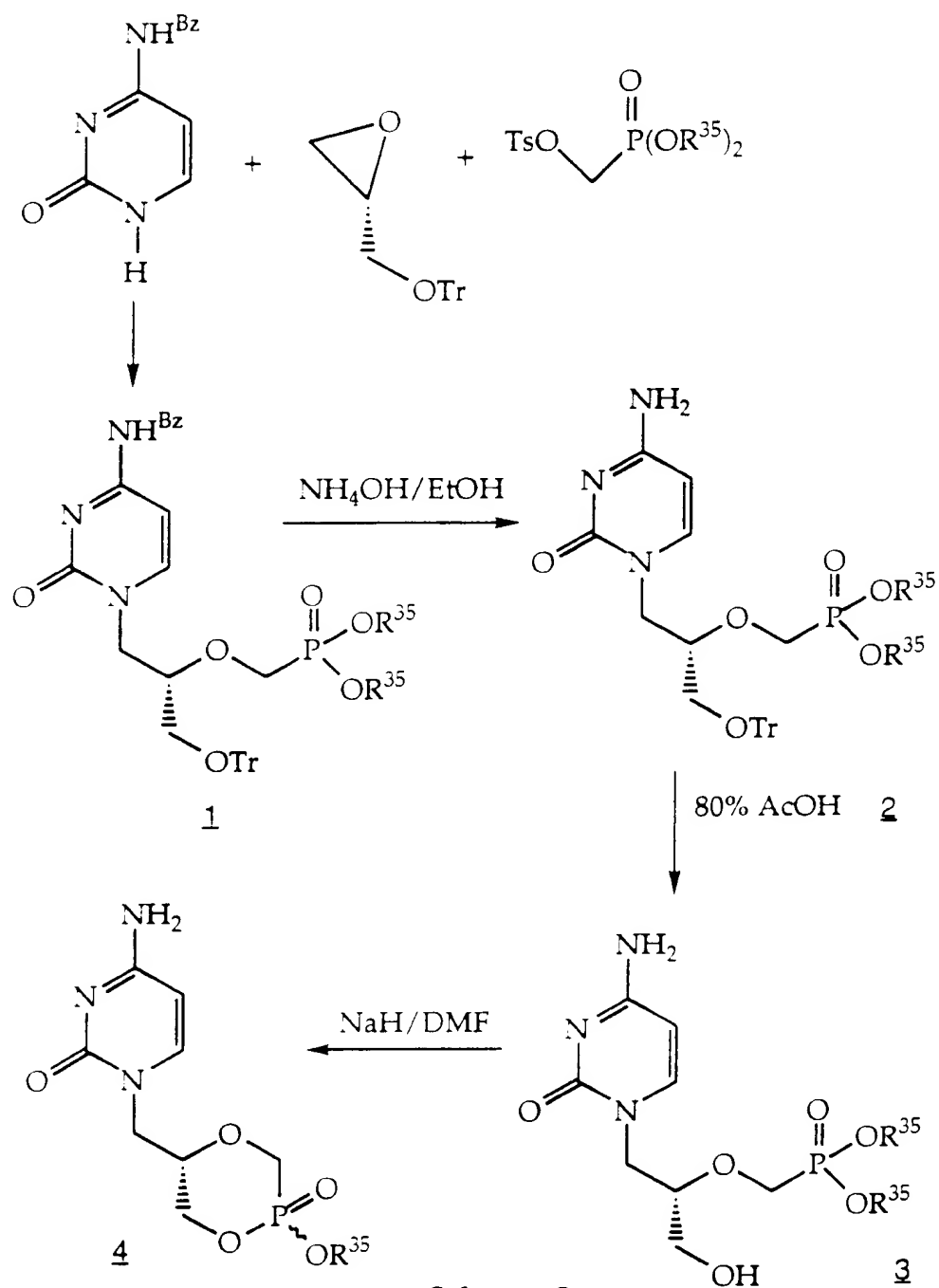
Substituted and unsubstituted alkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and other L^1 esters and amidates of cHPMPs typically are made by reacting the appropriate HPMP compound with SOCl_2/DMF to yield the activated phosphonylchloride (see Scheme 1), followed by treatment with the corresponding nucleophile (e.g. alkoxide, phenolate, amine, etc.) to yield the protected intermediate formamidine which is subsequently hydrolyzed to the target compound. Alternatively, esters can also be prepared as depicted in Scheme 2. The N-,O- protected intermediate phosphonate diester is obtained from the three building blocks by known methods. The N- and O- protecting groups are subsequently removed followed by treatment of the phosphonate diester **3** with NaH leading to cyclization yielding target compound **4**. A third method for the synthesis of cHSNA esters entails alkylation of the cHSNA using common alkylating agents D^1L (where L is a leaving group) such as alkyl halides, tosylates, diazoalkanes and the like (see Scheme 3). This method is particularly useful for preparing acyloxyalkyl esters by treatment of the cHSNA with the corresponding acyloxyalkylhalide. In an exemplary method for the preparation of acyloxyalkyl esters of cHPMPs, as shown in more detail in Example 12, DCC and $\text{R}^{45}\text{C}(\text{O})\text{OCH}_2\text{Cl}$ are reacted with the cyclic compound; but in contradistinction with prior methods the stoichiometric proportion of DCC: $\text{R}^{45}\text{C}(\text{O})\text{OCH}_2\text{Cl}$, cyclic HPMP is 1-2:1-2:1. Use of such low proportions of reactants lessens side reactions with any exocyclic amino group of B and thereby greatly improves yields. R^{45} is H or is

- C₃-C₁₂ alkyl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N and halogen, C₃-C₆ aryl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N and halogen or C₃-C₉ aryl-
- 5 alkyl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N and halogen.

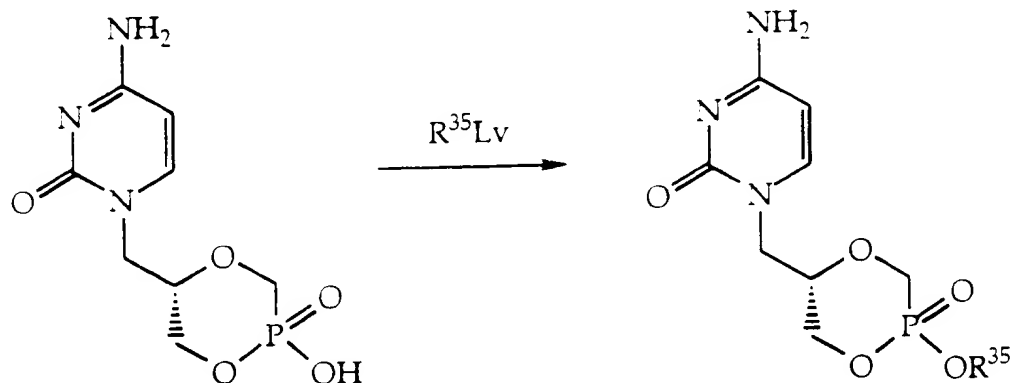
Each of the following schemes exemplify HPMPC as the nucleotide analog. However, any B is employed in place of cytosine, provided that any exocyclic oxo or amino groups are protected as required. Also, step 3 of

10 scheme 1 will be omitted when B contains no exocyclic amine.





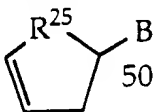
Scheme 2



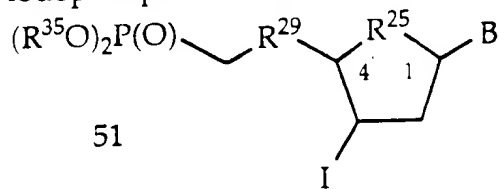
Scheme 3

A third method for the synthesis of cyclic HPMP esters entails alkylation of the cyclic HPMP ester as shown in Scheme 3 using common alkylating agents $R^{35}Lv$ (where Lv is a leaving group) such as alkyl halides, tosylates, diazoalkanes and the like. This method is particularly useful for preparing acyloxyalkyl esters by treatment of the cyclic HPMP (cHPMP) with the corresponding acyloxyalkylhalide.

Compounds where Z is of structure V and R^{25} and R^{29} is oxygen are synthesized by addition-elimination reaction using a compound of structure

50, , previously described for $B = \text{adenine}$ (EP 398 231) with iodine (about 2 equivalents) in organic solvent (such as acetonitrile or methylene chloride) at about $15-24^\circ \text{C}$ and a compound having the structure $(R^{35}O)_2P(O)-CH_2-OH$, wherein R^{35} is R or R^{31} (defined below), to yield the 3-

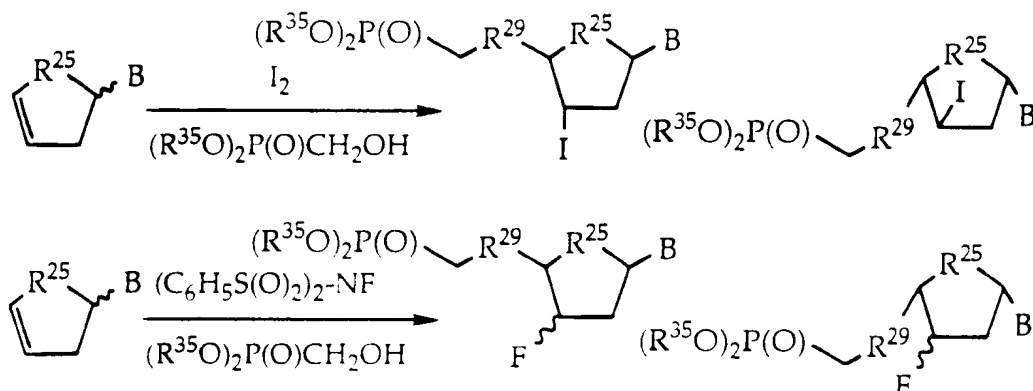
iodophosphonate diester of structure 51,



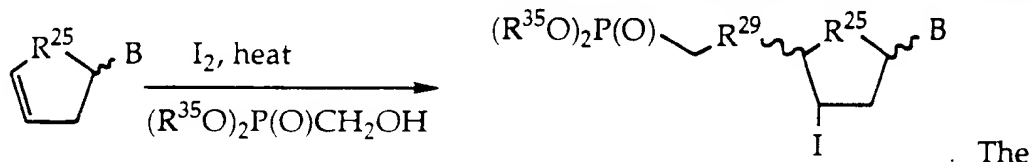
, which is then eliminated to yield the corresponding structure V compound by reaction with about 5 equivalents of a base such as sodium methoxide or DBU in anhydrous organic solvent such as methanol or tetrahydrofuran at room temperature for about 2-12 hours.

The following schemes show synthesis of intermediates having fluorine or iodine at the 3' position that are converted to structure V compounds by

elimination with a base. N-Fluorodibenzenesulfonamide is available commercially (Aldrich). Structure V compounds where B and the phosphonate ester substituent at the 4' position are either both up or down (i.e., substituents at the 1' and 4' positions are cis with respect to each other) are obtained by using the corresponding structure 50 reactant as follows

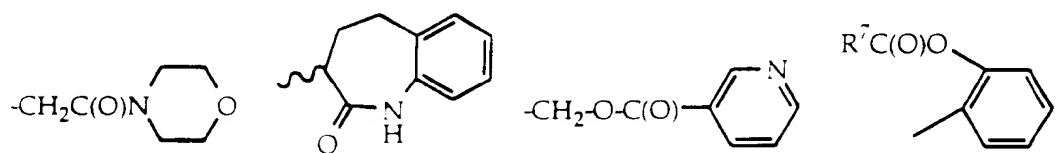


- 10 When the reaction with iodine is conducted at high temperature (about 50-80° C, usually about 60-70° C), a scalemic intermediate results as follows



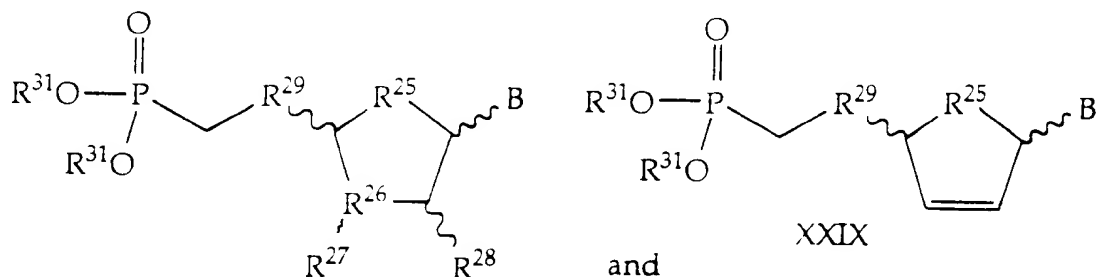
The intermediate is then converted to the corresponding structure V compound and the various cis and trans isomers can be separated using standard methods such as HPLC, RPLC or crystallization.

- Exemplary esters are of the formula, (R³¹O)₂P(O)-Z-B, (RO)(R³¹O)P(O)-Z-B or (RO)₂P(O)-Z-B, wherein R³¹ is independently 2,3-dihydro-6-hydroxyindene, sesamol, catechol monoester, -CH₂-C(O)-N(R⁷)₂ wherein each R⁷ is the same or different, -CH₂-S(O)(R⁷), -CH₂-S(O)₂(R⁷), -CH₂-CH(OC(O)CH₂R⁷)-CH₂(OC(O)CH₂R⁷), cholesteryl, a 5 or 6 carbon monosaccharide, disaccharide or oligosaccharide (3 to 9 monosaccharide residues), enolpyruvate (HOOC-C(=CH₂)O), glycerol, α-D-β-diglycerides (wherein the fatty acids composing glyceride lipids generally are naturally occurring saturated or unsaturated C₆₋₂₆, C₆₋₁₈ or C₆₋₁₀ fatty acids such as linoleic, lauric, myristic, palmitic, stearic, oleic, palmitoleic, linolenic and the like fatty acids), trimethoxybenzyl, triethoxybenzyl, 2-alkyl pyridinyl (C₁₋₄ alkyl),

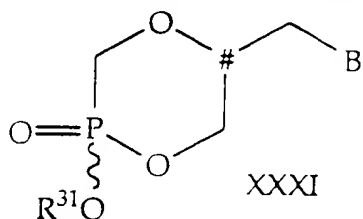


C₃-C₆ aryl (including phenyl, 2- and 3-pyrrolyl, 2- and 3-thienyl, 2- and 4-
 imidazolyl, 2-, 4- and 5-oxazolyl, 3- and 4-isoxazolyl, 2-, 4- and 5-thiazolyl, 3-,
 4- and 5-isothiazolyl, 3- and 4-pyrazolyl, 2-, 3- and 4-pyridinyl and 2-, 4- and 5-
 5 pyrimidinyl) substituted by 3, 4 or 5 halogen atoms or 1 or 2 atoms or groups
 selected from halogen, C₁-C₁₂ alkoxy (including methoxy, ethoxy, 2,3-, 2,4-,
 2,5-, 2,6-, 3,4- and 3,5-dimethoxy and 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-diethoxy
 substituted phenyl), cyano, nitro, OH, C₁-C₁₂ haloalkyl (1 to 6 halogen atoms),
 C₁-C₁₂ alkyl (including methyl and ethyl), C₂-C₁₂ alkenyl or C₂-C₁₂ alkynyl; or
 10 R³¹ is C₁-C₄ alkylene-C₃-C₆ aryl (including benzyl, -CH₂-pyrrolyl, -CH₂-
 thienyl, -CH₂-imidazolyl, -CH₂-oxazolyl, -CH₂-isoxazolyl, -CH₂-thiazolyl,
 -CH₂-isothiazolyl, -CH₂-pyrazolyl, -CH₂-pyridinyl and -CH₂-pyrimidinyl)
 substituted in the aryl moiety by 3 to 5 halogen atoms or 1 to 2 atoms or
 groups selected from halogen, C₁-C₁₂ alkoxy (including methoxy and ethoxy),
 15 cyano, nitro, OH, C₁-C₁₂ haloalkyl (1 to 6 halogen atoms; including -CH₂-
 CCl₃), C₁-C₁₂ alkyl (including methyl and ethyl), C₂-C₁₂ alkenyl or C₂-C₁₂
 alkynyl. Methods for linking cholesteryl, saccharide and other moieties to
 reactive groups have been described (Hadfield Adv. Pharmacol. Chemother.
 (1984) 20:21; Gouyette Tet. Lett. (1989) 30:6019; Ksander J. Med. Chem. (1994)
 20 37:1823).

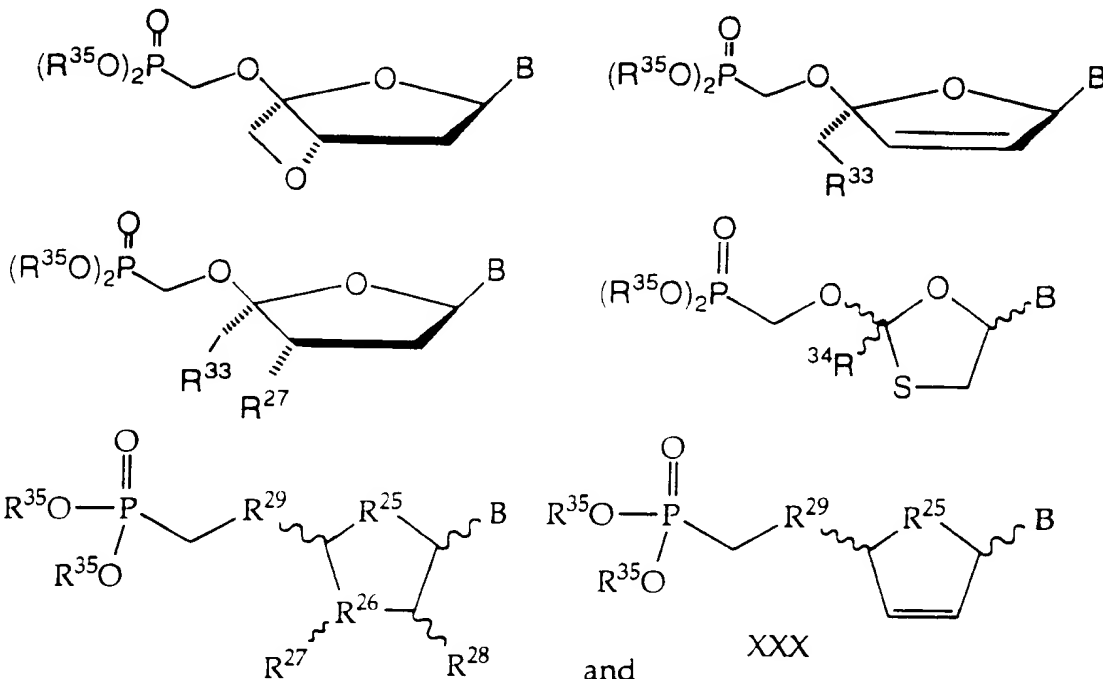
The compounds are used as intermediates in the synthesis of mixed
 amidate-ester nucleotide analog amidates, or in some cases, as drugs *per se*.
 Additional exemplary ester compounds have the formulas (R³¹O)₂P(O)-Z¹-B
 or (RO)(R³¹O)P(O)-Z¹-B, where Z¹ is defined to mean the substructure in the
 25 following representative structures; (R³¹O)₂-P(O)-CH₂-O-CH₂-CH₂-B, (R³¹O)₂-
 P(O)-CH₂-O-C#H(CH₂OH)-CH₂-B, (R³¹O)₂-P(O)-CH₂-O-C#H(CH₃)-CH₂-B,
 (R³¹O)₂-P(O)-CH₂-O-C#H(CH₂F)-CH₂-B, (R³¹O)₂-P(O)-CH₂-O-C#H(CH=CH₂)-
 CH₂-B, (R³¹O)₂-P(O)-CH₂-O-C#H(CH₂N₃)-CH₂-B,



where C#, R²⁵ - R²⁹, R³¹ and B have the meanings previously defined with the proviso that PMEA bis(4-nitrobenzyl ester) and PMEA bis(4-trifluoromethyl ester) are excluded and for structure XXIX, R²⁹ and R²⁵ are both O. Additional ester and nucleotide compounds are of the formula



where substituents linked to the carbon atom designated # are in the *R*, *S* or *RS* configuration and R³¹ and B are as previously defined. Nucleotides and esters of the formulas



wherein #, B, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, R³¹, R³³ and R³⁴ are as defined, R³⁵ is defined as R or R³¹ and for structure XXX, when R²⁹ is CH₂ or O and R²⁵ is CH₂ or O, R³⁵ is not H or C₁-C₆ alkyl, are new. Compounds having R³⁵

include species where both R³⁵ are both H and their salts including pharmaceutically acceptable salts.

Exemplary R³¹ include 2-, 3- and 4-alkoxyphenyl (C₁-C₁₂ alkyl including 2-, 3- and 4-methoxyphenyl and 2-, 3- and 4-ethoxyphenyl), 2-, 3- and 4-carboethoxyphenyl, 2- and 3-carboethoxy-4-hydroxyphenyl, 2- and 3-ethoxy-4-hydroxyphenyl, 2- and 3-ethoxy-5-hydroxyphenyl, 2- and 3-ethoxy-6-hydroxyphenyl, 2-, 3- and 4-O-acetylphenyl, 2-, 3- and 4-dimethylaminophenyl, 2-, 3- and 4-methylmercaptophenyl, 2-, 3- and 4-halophenyl (including 2-, 3- and 4-fluorophenyl and 2-, 3- and 4-chlorophenyl), 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-biscarboxyethylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dihalophenyl (including 2,4-difluorophenyl and 3,5-difluorophenyl), 2-, 3- and 4-haloalkylphenyl (1 to 5 halogen atoms, C₁-C₁₂ alkyl including 4-trifluoromethylphenyl), 2-, 3- and 4-cyanophenyl, and 2-, 3- and 4-nitrophenyl, 2-, 3- and 4-haloalkylbenzyl (1 to 5 halogen atoms, C₁-C₁₂ alkyl including 4-trifluoromethylbenzyl), α -D-galactose, α -D-glucose, α -D-fructose. The bis esters of formula (OR³¹)(OR³¹)P(O)-Z-B and (OR)(OR³¹)P(O)-Z-B are novel and are useful as intermediates in the synthesis of the mixed amidate-ester nucleotide analog amides of the invention. These compounds can also be used directly as antimicrobial agents per se. Table 5 lists a group of exemplary bis esters of compounds having the structure (OR³⁵)₂P(O)-Z-B which includes novel compounds of structure (OR³¹)₂P(O)-Z-B.

TABLE 5

OR ^{35*}	-P(O)-Z-B**
30 1 -O-C ₆ H ₄ F	1 -P(O)-CH ₂ -O-CH ₂ -CH ₂ -B
2 -O-C ₆ H ₃ F ₂	2 -P(O)-CH ₂ -O-C [#] H(CH ₂ -OR ⁴)-CH ₂ -B
3 -O-C ₆ H ₄ -OCH ₃	3 -P(O)-CH ₂ -O-C [#] H(CH ₃)-CH ₂ -B
4 -O-C ₆ H ₃ -(OCH ₃) ₂	4 -P(O)-CH ₂ -O-C [#] H(CH ₂ F)-CH ₂ -B
5 -O-C ₆ H ₄ -OC ₂ H ₅	5 -P(O)-CH ₂ -O-C [#] H(CH=CH ₂)-CH ₂ -B
35 6 -O-C ₆ H ₃ -(OC ₂ H ₅) ₂	6 -P(O)-CH ₂ -O-C [#] H(CH ₂ N ₃)-CH ₂ -B

- 7 -O-CH₂-C₆H₄F 7 **
 8 -O-C₆H₄-(C(O)-O-C₂H₅)₂ 8 **
 9 -O-C₆H₄-C(O)-O-C₂H₅
 5 10 -O-C₆H₃-(O-C(O)-CH₃)₂
 11 -O-C₆H₃-C(O)-O-C₃H₇
 12 -O-CH₂-C₆H₄-O-CO-CH₃
 13 -O-C₅H₄N
 14 -O-C₆H₃-(OC₂H₅)(OH)
 10 15 -O-C₆H₅
 16 -O-CH₂-O-C(O)-C(CH₃)₃

B

- 1 adenin-9-yl
 2 guanin-9-yl
 15 3 cytosin-1-yl
 4 2, 6-diaminopurin-9-yl
 5 2-aminopurin-9-yl
 6 thymidin-1-yl
 7 5-fluorocytosin-1-yl

20

* Monosubstituted phenyl and benzyl compounds (i.e., R³⁵ numbers 1, 3, 5, etc) include 2-, 3- and 4-substituted compounds and disubstituted phenyl compounds (i.e., R³⁵ numbers 2, 4, 6, etc) include 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-substituted compounds.

- 25 ** The structure =P(O)- indicates that two bonds are occupied by OR³⁵; Z structure 7 is of formula IV where R²⁵ and R²⁹ are O, R²⁶ is S, R²⁷ is absent and R²⁸ is H and includes the (+) and (-) enantiomers; structure 8 is of formula V where R²⁵ and R²⁹ are O.

- 30 Compounds listed in Table 5 are designated herein by numbers assigned to (OR³⁵)₂ (where each R³⁵ is the same), Z and B according to the following convention, R³⁵.Z.B. Exemplary compounds include 1.1.1, 2.1.1, 3.1.1, 4.1.1, 5.1.1, 6.1.1, 7.1.1, 8.1.1, 9.1.1, 10.1.1, 11.1.1, 12.1.1, 13.1.1, 14.1.1, 15.1.1, 16.1.1, 1.2.1, 2.2.1, 3.2.1, 4.2.1, 5.2.1, 6.2.1, 7.2.1, 8.2.1, 9.2.1, 10.2.1, 11.2.1, 12.2.1, 13.2.1, 14.2.1, 15.2.1, 16.2.1, 1.3.1, 2.3.1, 3.3.1, 4.3.1, 5.3.1, 6.3.1, 7.3.1, 8.3.1, 9.3.1, 10.3.1, 11.3.1, 12.3.1, 13.3.1, 14.3.1, 15.3.1, 16.3.1, 1.4.1, 2.4.1, 3.4.1, 4.4.1, 5.4.1, 6.4.1,

7.4.1, 8.4.1, 9.4.1, 10.4.1, 11.4.1, 12.4.1, 13.4.1, 14.4.1, 15.4.1, 16.4.1, 1.5.1, 2.5.1, 3.5.1,
 4.5.1, 5.5.1, 6.5.1, 7.5.1, 8.5.1, 9.5.1, 10.5.1, 11.5.1, 12.5.1, 13.5.1, 14.5.1, 15.5.1, 16.5.1,
 1.6.1, 2.6.1, 3.6.1, 4.6.1, 5.6.1, 6.6.1, 7.6.1, 8.6.1, 9.6.1, 10.6.1, 11.6.1, 12.6.1, 13.6.1,
 14.6.1, 15.6.1, 16.6.1, 1.7.1, 2.7.1, 3.7.1, 4.7.1, 5.7.1, 6.7.1, 7.7.1, 8.7.1, 9.7.1, 10.7.1,
 5 11.7.1, 12.7.1, 13.7.1, 14.7.1, 15.7.1, 16.7.1, 1.8.1, 2.8.1, 3.8.1, 4.8.1, 5.8.1, 6.8.1, 7.8.1,
 8.8.1, 9.8.1, 10.8.1, 11.8.1, 12.8.1, 13.8.1, 14.8.1, 15.8.1, 16.8.1, 1.1.2, 2.1.2, 3.1.2, 4.1.2,
 5.1.2, 6.1.2, 7.1.2, 8.1.2, 9.1.2, 10.1.2, 11.1.2, 12.1.2, 13.1.2, 14.1.2, 15.1.2, 16.1.2, 1.2.2,
 2.2.2, 3.2.2, 4.2.2, 5.2.2, 6.2.2, 7.2.2, 8.2.2, 9.2.2, 10.2.2, 11.2.2, 12.2.2, 13.2.2, 14.2.2,
 15.2.2, 16.2.2, 1.3.2, 2.3.2, 3.3.2, 4.3.2, 5.3.2, 6.3.2, 7.3.2, 8.3.2, 9.3.2, 10.3.2, 11.3.2,
 10 12.3.2, 13.3.2, 14.3.2, 15.3.2, 16.3.2, 1.4.2, 2.4.2, 3.4.2, 4.4.2, 5.4.2, 6.4.2, 7.4.2, 8.4.2,
 9.4.2, 10.4.2, 11.4.2, 12.4.2, 13.4.2, 14.4.2, 15.4.2, 16.4.2, 1.5.2, 2.5.2, 3.5.2, 4.5.2, 5.5.2,
 6.5.2, 7.5.2, 8.5.2, 9.5.2, 10.5.2, 11.5.2, 12.5.2, 13.5.2, 14.5.2, 15.5.2, 16.5.2, 1.6.2, 2.6.2,
 3.6.2, 4.6.2, 5.6.2, 6.6.2, 7.6.2, 8.6.2, 9.6.2, 10.6.2, 11.6.2, 12.6.2, 13.6.2, 14.6.2, 15.6.2,
 16.6.2, 1.7.2, 2.7.2, 3.7.2, 4.7.2, 5.7.2, 6.7.2, 7.7.2, 8.7.2, 9.7.2, 10.7.2, 11.7.2, 12.7.2,
 15 13.7.2, 14.7.2, 15.7.2, 16.7.2, 1.8.2, 2.8.2, 3.8.2, 4.8.2, 5.8.2, 6.8.2, 7.8.2, 8.8.2, 9.8.2,
 10.8.2, 11.8.2, 12.8.2, 13.8.2, 14.8.2, 15.8.2, 16.8.2, 1.1.3, 2.1.3, 3.1.3, 4.1.3, 5.1.3, 6.1.3,
 7.1.3, 8.1.3, 9.1.3, 10.1.3, 11.1.3, 12.1.3, 13.1.3, 14.1.3, 15.1.3, 16.1.3, 1.2.3, 2.2.3, 3.2.3,
 4.2.3, 5.2.3, 6.2.3, 7.2.3, 8.2.3, 9.2.3, 10.2.3, 11.2.3, 12.2.3, 13.2.3, 14.2.3, 15.2.3, 16.2.3,
 1.3.3, 2.3.3, 3.3.3, 4.3.3, 5.3.3, 6.3.3, 7.3.3, 8.3.3, 9.3.3, 10.3.3, 11.3.3, 12.3.3, 13.3.3,
 20 14.3.3, 15.3.3, 16.3.3, 1.4.3, 2.4.3, 3.4.3, 4.4.3, 5.4.3, 6.4.3, 7.4.3, 8.4.3, 9.4.3, 10.4.3,
 11.4.3, 12.4.3, 13.4.3, 14.4.3, 15.4.3, 16.4.3, 1.5.3, 2.5.3, 3.5.3, 4.5.3, 5.5.3, 6.5.3, 7.5.3,
 8.5.3, 9.5.3, 10.5.3, 11.5.3, 12.5.3, 13.5.3, 14.5.3, 15.5.3, 16.5.3, 1.6.3, 2.6.3, 3.6.3, 4.6.3,
 5.6.3, 6.6.3, 7.6.3, 8.6.3, 9.6.3, 10.6.3, 11.6.3, 12.6.3, 13.6.3, 14.6.3, 15.6.3, 16.6.3, 1.7.3,
 2.7.3, 3.7.3, 4.7.3, 5.7.3, 6.7.3, 7.7.3, 8.7.3, 9.7.3, 10.7.3, 11.7.3, 12.7.3, 13.7.3, 14.7.3,
 25 15.7.3, 16.7.3, 1.8.3, 2.8.3, 3.8.3, 4.8.3, 5.8.3, 6.8.3, 7.8.3, 8.8.3, 9.8.3, 10.8.3, 11.8.3,
 12.8.3, 13.8.3, 14.8.3, 15.8.3, 16.8.3, 1.1.4, 2.1.4, 3.1.4, 4.1.4, 5.1.4, 6.1.4, 7.1.4, 8.1.4,
 9.1.4, 10.1.4, 11.1.4, 12.1.4, 13.1.4, 14.1.4, 15.1.4, 16.1.4, 1.2.4, 2.2.4, 3.2.4, 4.2.4, 5.2.4,
 6.2.4, 7.2.4, 8.2.4, 9.2.4, 10.2.4, 11.2.4, 12.2.4, 13.2.4, 14.2.4, 15.2.4, 16.2.4, 1.3.4, 2.3.4,
 3.3.4, 4.3.4, 5.3.4, 6.3.4, 7.3.4, 8.3.4, 9.3.4, 10.3.4, 11.3.4, 12.3.4, 13.3.4, 14.3.4, 15.3.4,
 30 16.3.4, 1.4.4, 2.4.4, 3.4.4, 4.4.4, 5.4.4, 6.4.4, 7.4.4, 8.4.4, 9.4.4, 10.4.4, 11.4.4, 12.4.4,
 13.4.4, 14.4.4, 15.4.4, 16.4.4, 1.5.4, 2.5.4, 3.5.4, 4.5.4, 5.5.4, 6.5.4, 7.5.4, 8.5.4, 9.5.4,
 10.5.4, 11.5.4, 12.5.4, 13.5.4, 14.5.4, 15.5.4, 16.5.4, 1.6.4, 2.6.4, 3.6.4, 4.6.4, 5.6.4, 6.6.4,
 7.6.4, 8.6.4, 9.6.4, 10.6.4, 11.6.4, 12.6.4, 13.6.4, 14.6.4, 15.6.4, 16.6.4, 1.7.4, 2.7.4, 3.7.4,
 4.7.4, 5.7.4, 6.7.4, 7.7.4, 8.7.4, 9.7.4, 10.7.4, 11.7.4, 12.7.4, 13.7.4, 14.7.4, 15.7.4, 16.7.4,
 35 1.8.4, 2.8.4, 3.8.4, 4.8.4, 5.8.4, 6.8.4, 7.8.4, 8.8.4, 9.8.4, 10.8.4, 11.8.4, 12.8.4, 13.8.4,

14.8.4, 15.8.4, 16.8.4, 1.1.5, 2.1.5, 3.1.5, 4.1.5, 5.1.5, 6.1.5, 7.1.5, 8.1.5, 9.1.5, 10.1.5,
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 8.2.5, 9.2.5, 10.2.5, 11.2.5, 12.2.5, 13.2.5, 14.2.5, 15.2.5, 16.2.5, 1.3.5, 2.3.5, 3.3.5, 4.3.5,
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 5 2.4.5, 3.4.5, 4.4.5, 5.4.5, 6.4.5, 7.4.5, 8.4.5, 9.4.5, 10.4.5, 11.4.5, 12.4.5, 13.4.5, 14.4.5,
 15.4.5, 16.4.5, 1.5.5, 2.5.5, 3.5.5, 4.5.5, 5.5.5, 6.5.5, 7.5.5, 8.5.5, 9.5.5, 10.5.5, 11.5.5,
 12.5.5, 13.5.5, 14.5.5, 15.5.5, 16.5.5, 1.6.5, 2.6.5, 3.6.5, 4.6.5, 5.6.5, 6.6.5, 7.6.5, 8.6.5,
 9.6.5, 10.6.5, 11.6.5, 12.6.5, 13.6.5, 14.6.5, 15.6.5, 16.6.5, 1.7.5, 2.7.5, 3.7.5, 4.7.5, 5.7.5,
 6.7.5, 7.7.5, 8.7.5, 9.7.5, 10.7.5, 11.7.5, 12.7.5, 13.7.5, 14.7.5, 15.7.5, 16.7.5, 1.8.5, 2.8.5,
 10 3.8.5, 4.8.5, 5.8.5, 6.8.5, 7.8.5, 8.8.5, 9.8.5, 10.8.5, 11.8.5, 12.8.5, 13.8.5, 14.8.5, 15.8.5,
 16.8.5, 1.1.6, 2.1.6, 3.1.6, 4.1.6, 5.1.6, 6.1.6, 7.1.6, 8.1.6, 9.1.6, 10.1.6, 11.1.6, 12.1.6,
 13.1.6, 14.1.6, 15.1.6, 16.1.6, 1.2.6, 2.2.6, 3.2.6, 4.2.6, 5.2.6, 6.2.6, 7.2.6, 8.2.6, 9.2.6,
 10.2.6, 11.2.6, 12.2.6, 13.2.6, 14.2.6, 15.2.6, 16.2.6, 1.3.6, 2.3.6, 3.3.6, 4.3.6, 5.3.6, 6.3.6,
 7.3.6, 8.3.6, 9.3.6, 10.3.6, 11.3.6, 12.3.6, 13.3.6, 14.3.6, 15.3.6, 16.3.6, 1.4.6, 2.4.6, 3.4.6,
 15 4.4.6, 5.4.6, 6.4.6, 7.4.6, 8.4.6, 9.4.6, 10.4.6, 11.4.6, 12.4.6, 13.4.6, 14.4.6, 15.4.6, 16.4.6,
 1.5.6, 2.5.6, 3.5.6, 4.5.6, 5.5.6, 6.5.6, 7.5.6, 8.5.6, 9.5.6, 10.5.6, 11.5.6, 12.5.6, 13.5.6,
 14.5.6, 15.5.6, 16.5.6, 1.6.6, 2.6.6, 3.6.6, 4.6.6, 5.6.6, 6.6.6, 7.6.6, 8.6.6, 9.6.6, 10.6.6,
 11.6.6, 12.6.6, 13.6.6, 14.6.6, 15.6.6, 16.6.6, 1.7.6, 2.7.6, 3.7.6, 4.7.6, 5.7.6, 6.7.6, 7.7.6,
 8.7.6, 9.7.6, 10.7.6, 11.7.6, 12.7.6, 13.7.6, 14.7.6, 15.7.6, 16.7.6, 1.8.6, 2.8.6, 3.8.6, 4.8.6,
 20 5.8.6, 6.8.6, 7.8.6, 8.8.6, 9.8.6, 10.8.6, 11.8.6, 12.8.6, 13.8.6, 14.8.6, 15.8.6, 16.8.6, 1.1.7,
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 25 6.4.7, 7.4.7, 8.4.7, 9.4.7, 10.4.7, 11.4.7, 12.4.7, 13.4.7, 14.4.7, 15.4.7, 16.4.7, 1.5.7, 2.5.7,
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 16.5.7, 1.6.7, 2.6.7, 3.6.7, 4.6.7, 5.6.7, 6.6.7, 7.6.7, 8.6.7, 9.6.7, 10.6.7, 11.6.7, 12.6.7,
 13.6.7, 14.6.7, 15.6.7, 16.6.7, 1.7.7, 2.7.7, 3.7.7, 4.7.7, 5.7.7, 6.7.7, 7.7.7, 8.7.7, 9.7.7,
 10.7.7, 11.7.7, 12.7.7, 13.7.7, 14.7.7, 15.7.7, 16.7.7, 1.8.7, 2.8.7, 3.8.7, 4.8.7, 5.8.7, 6.8.7,
 30 7.8.7, 8.8.7, 9.8.7, 10.8.7, 11.8.7, 12.8.7, 13.8.7, 14.8.7, 15.8.7 and 16.8.7.

Exemplary bis esters include bis(pivaloyloxymethyl)PMEA (i.e.
 bis(pivaloyloxymethyl)-9-(2-phosphonylmethoxyethyl)adenine),
 bis(pivaloyloxymethyl)HPMPC, bis(pivaloyloxymethyl)D4AMPI,
 bis(pivaloyloxymethyl)D4TMPI, bis(N-ethylmorpholino)PMEA, bis(N-
 35 ethylmorpholino)HPMPC, bis(N-ethylmorpholino)PMPDAP, bis(N-

ethylmorpholino)HPMPA, bis(N-ethylmorpholino)PMEG, bis(N-ethylmorpholino)D4AMPI, bis(N-ethylmorpholino)D4TMPI, bis(phenyl)PMEA, bis(phenyl)HPMPC, bis(phenyl)HPMPA, bis(phenyl)D4AMPI, bis(phenyl)D4TMPI, bis(t-butyl)PMEA, bis(t-butyl)D4AMPI, bis(t-butyl)D4TMPI, bis(t-butyl)HPMPC, bis(2-ethoxyphenyl)PMEA, bis(2-ethoxyphenyl)HPMPC, , bis(4-fluorophenyl)PMEA, bis(4-fluorophenyl)HPMPC, bis(3,5-dimethoxyphenyl)PMEA, bis(3,5-dimethoxyphenyl)HPMPC and the like. L¹ is an amino acid which is, in general, esterified at free α -carboxyl group(s) by R⁴, or is a dipeptide, tripeptide or oligopeptide which is optionally esterified at the free α -carboxyl group by R⁴. L² is an ester or thioester group. Suitable L² esters (and the corresponding thioesters) include methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, t-butyl ester, phenyl ester, benzyl ester, N-ethylmorpholino ester (-O-CH₂-CH₂-N[(CH₂)₂(CH₂)₂O]), pivaloyloxymethyl ester (-O-CH₂-O-C(O)-C(CH₃)₃) and the like. The suitability of the presence or absence of any particular L² or R⁴ group is determined by stability and/or bioavailability assays (e.g., stability assay in aqueous conditions such as low pH/intestinal lumen conditions or assay in the presence of cellular extracts containing esterases or by bioavailability assay using animal models) known in the art. These assays are routinely performed by the skilled artisan.

The bis ester is then converted to a monoester by chemical hydrolysis in base or acid according to the bis ester used. For example, treatment with NaOH (0.5 to 2 N) or NH₄OH in a solvent such as THF (tetrahydrofuran), dioxane or an alcohol for 1 to 24 hours at 22° to 90° is suitable for most esters. The choice of solvent will depend on the characteristics of the bis ester used. The stability of the ester groups of phosphonate bis esters and phosphonate bis thioesters toward hydrolysis is unequal and provides a means for obtaining the monoester. Selection of hydrolysis conditions is determined by routine testing. Alkaline hydrolysis yields the phosphonate monoester and a corresponding alcohol or phenol. L¹ is then linked to the monoester or monothioester using reagents and conditions (i.e., a 1:1 mixture of triphenylphosphine (PPh₃) and 2,2'-dipyridyl disulfide in a suitable solvent such as pyridine or DMF) essentially as described for synthesis of bis amidates.

Nucleoside bis esters of formulas VI, VII and VIII compounds are shown in Figures 4 - 7. 3',4'-Unsaturated nucleosides that are used as a starting material was previously described (Zemlicka, et al J Am Chem Soc (1970) 92:4744-4745). 4'-Modified nucleosides have also been described (Yang, et al Tet Lett (1992) 33: 41-44; Yang, et al Tet Lett (1992) 33: 37-40; Prisbe, et al Nucleosides and Nucleotides as Antitumor and Antiviral Agents (1993) Plenum Press, New York, Chu, C.K. et al eds., p. 101-113). The phosphonate ester is condensed with the unsaturated nucleoside using an oxidizing agent such as MCPBA (m-chloroperoxybenzoic acid), IBr or N-iodosuccinimide (NIS). The choice of a particular oxidizing agent will be guided by considerations such as the type of heterocyclic base or sugar substituent that is present. For example, IBr may not be generally compatible with a substituent such as azide (at R²⁷ or R³³) or 1-propynyl (at B). In these cases, NIS or MCPBA is used. A further example is reduction of the 2',3'-double bond using H₂/Pd/C, which is generally not compatible with an alkynyl group that can be present at B. In this case, the alkynyl group would be added to an appropriate heterocyclic base (a purine such as 7-deaza-7-iodoadenine or 7-deaza-7-iodoguanine, etc or a pyrimidine such as 5-iodocytosine, 5-iodouracil, uracil, etc) that is later converted to the alkynyl derivative (7-deaza-7-(1-propynyl)adenine, 5-(1-propynyl)uracil, etc) using an alkyne such as propyne and palladium (08/050,698; PCT/US92/10115; Hobbs et al, J Org Chem (1989) 54:3420-3422). For Figures 3 - 7, R³³ is H, OH, TBSO, halogen, cyano, CH₂N₃, C₁-C₄ alkyl, C₁-C₄ alkoxy (including OCH₃), CH₂OH or azido; R³⁴ is H, OH halogen (fluorine is preferred), azide, O-alkyl (C₁-C₆ including O-methyl and O-ethyl), S-alkyl (C₁-C₆ including S-methyl and S-ethyl) and O-alkenyl (including O-allyl); R is as defined above, except that for the structure (RO)₂P(O)-CH₂-OH, R is not hydrogen, and R includes C₁-C₂₀ alkoxyacyl groups including methoxyacyl (pivaloyloxymethyl, adamantoyl oxymethyl and the like) and ethoxyacyl (pivaloyloxyethyl and the like) moieties; TBSO is t-butyldimethylsilyl ether. The phosphonates and monoesters shown in Figures 4 - 7 are converted to bis amidates or mixed amidate ester compounds using reagents and conditions (e.g., a 1:1 mixture of triphenylphosphine (PPh₃) and 2,2'-dipyridyl disulfide in a suitable solvent such as pyridine or DMF) essentially as described above.

Mixed bis amidate synthesis. Synthesis of compounds of formula Id where L^1 and L^2 are both amino acids or where L^1 is an amino acid and L^2 is an amine (NH_2 , NHR^6 , $N(R^6)_2$) but are not both the same is accomplished by direct conversion as described above for bis amidates followed by separation of the final products. Another method to synthesize mixed bis amidates is amidation of an appropriate phosphonate monoester to give a compound of formula Id, followed by removal of the ester group under conditions that do not remove the first amide. Synthesis of phosphonate monoester compounds has been described (EP 481 214). This compound is then converted to a mixed bis amide by condensation with a second amino acid to yield the final product as described (i.e., using a 1:1 mixture of triphenylphosphine and 2,2'-dipyridyl disulfide).

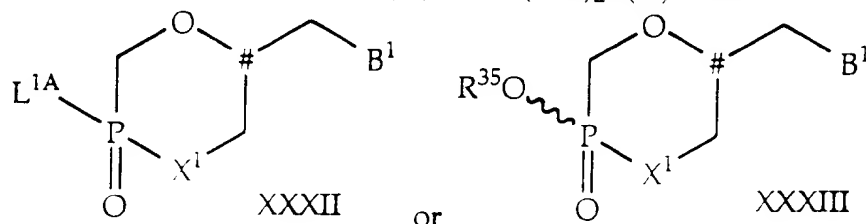
Mono amidate synthesis. Synthesis of compounds of formula Ib where L^1 is an amino acid and X^1 is O (oxygen) is accomplished essentially as described for bis amidate synthesis using a cyclic nucleotide analog such as cHPMPC (cyclic HPMP), cHPMPA, cHPMPDAP, cHPMPG and the like. Cyclic HPMP series compounds (cHPMPC, etc) are prepared by direct dehydration of the corresponding HPMP nucleotide analog using DCC (dicyclohexylcarbodiimide) or using 4-morpholino-N,N'-dicyclohexylcarboxamide as described (Ho et al Mol Pharmacol (1992) 41:197-202). The cyclic phosphonate is condensed with an optionally protected amino acid ester in the presence of a 1:1 mixture of triphenylphosphine and 2,2'-dipyridyl disulfide in a suitable solvent such as pyridine or DMF.

Synthesis of formula Ib compounds where X^1 is S is accomplished as shown in Figure 1. Conversion of the six-membered heterocycle to an amidate is accomplished in essentially the same manner as described (i.e., using triphenylphosphine and 2,2'-dipyridyl disulfide).

Synthesis of formula IV compounds where R^{26} is S and R^{25} and R^{29} are O is accomplished as shown in Figure 3. The starting material is synthesized by reaction of thiolacetic acid (Aldrich Cat. No. T3,080-5), bromoacetaldehyde diethyl acetal (Aldrich Cat. No. 12,398-6) and potassium tert-butoxide (Aldrich Cat. No. 15,667-1) in DMF. Synthesis of **1** where R^{34} is H is accomplished using neat $(EtO)_3CH$. Synthesis of **1** where R^{34} is CH_2CN or CF_3 is accomplished using $(EtO)_3CH_2CN$ or $(EtO)_3CF_3$ in methylene chloride with a

catalytic acid (such as p-toluenesulfonic acid). Conversion of the thiaorthoester **1** to the phosphonate **2** is accomplished using an acid such as tosic acid or perchloric acid in catalytic amounts. The resulting bis ester is then converted to a bis amidate in essentially the same manner as described (i.e., using triphenylphosphine and 2,2'-dipyridyl disulfide). Mixed ester-amidate compounds are obtained by removing a single ester from the bis ester using base (NaOH, NH₄OH, etc) as described. The phosphonate **3** is obtained by treatment with a base such as TMSBr or TMSI in a solvent (such as methylene chloride, DMF or acetonitrile) in the presence of lutidine (where R is alkyl, aryl or substituted aryl, acyloxyalkyl such as isopropyl, phenyl, 2-ethoxyphenyl) or by treatment with Pd/C/H₂ (where R is alkaryl or substituted alkaryl such as benzyl and the like). R³⁴ in Figure 3 is H, CF₃ or CH₂CN.

Protected heterocyclic base compounds. The present invention includes nucleotide analogs that comprise a protected heterocyclic base. These compounds are useful as synthetic intermediates and/or, as therapeutic agents *per se*. Protected heterocyclic base compounds structures, their isomers, tautomers and the salts of such compounds having the formula (R³⁵O)₂P(O)-Z-B¹, (L^{1A}O)(L^{2A}O)P(O)-Z-B¹, (HO)₂P(O)-Z-B¹



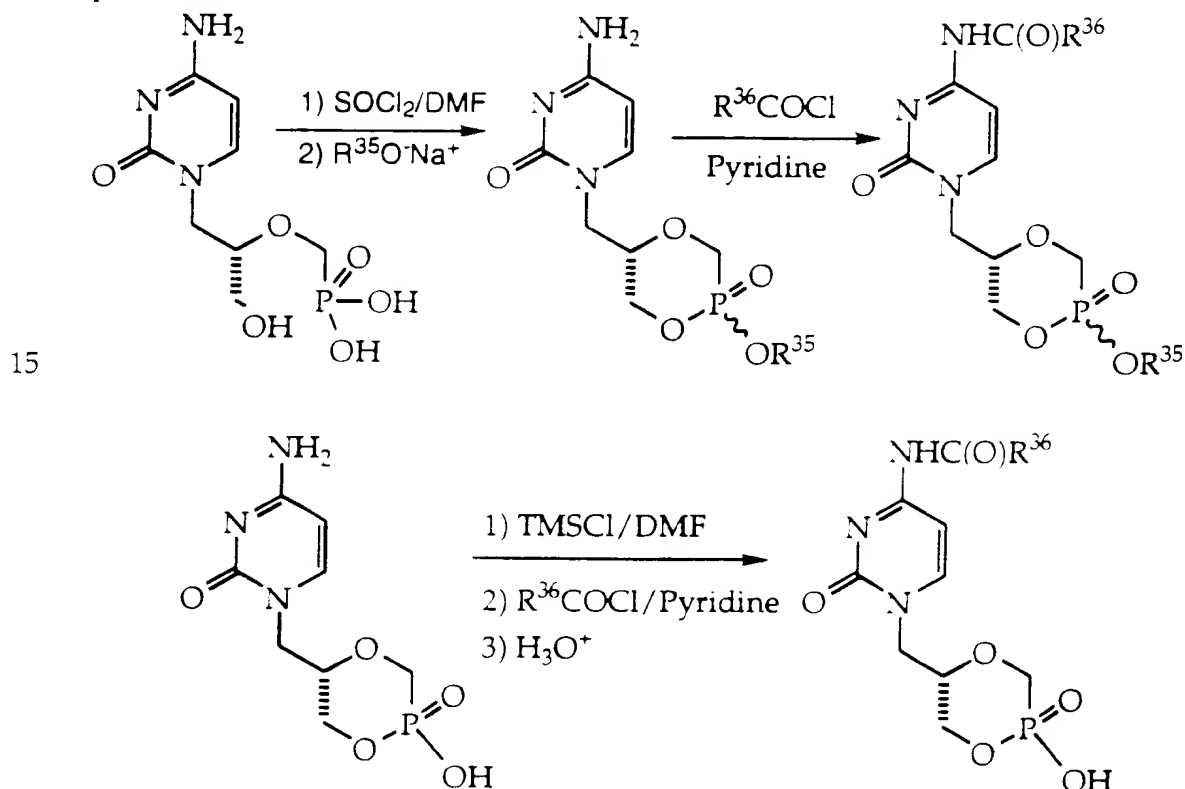
where L^{1A} is L¹, R or NHR⁴⁰, wherein R⁴⁰ is C₁-C₂₀ alkyl; L^{2A} is L², R³⁵ or NHR⁴⁰; B¹ is a protected heterocyclic base having the formula Xa, XIa, XIb, XIIa or XIIIa previously defined.

Suitable exemplary Z include compounds of formulas IV, V, VI, VII, VIII, -CH₂-O-CH₂-CH₂-, -CH₂-O-C#H(CH₃)-CH₂- and -CH₂-O-C#H(CH₂OH)-CH₂- having a heterocyclic base with an exocyclic amine can be converted to nucleotide analog amidates or esters comprising a protected heterocyclic base either by reacting the nucleotide analog amidate or ester with R³⁶C(O)Cl or (CH₃O)₂CHR³⁸. Protected heterocyclic bases include species having protecting groups at exocyclic amine groups such as the N⁴-amine of cytosine, the N⁶-

amine of adenine and the N²-amine of guanine. The phosphonate moiety of compounds containing B¹ may be present as an ester, an amidate or as the free acid.

5 Bases having NHR⁴⁰ at an exocyclic amine are synthesized to obtain a protected pyrimidine or purine essentially as described (Gilliam Anal. Biochem. (1986) 157:199; Gallo-Rodriguez J. Med. Chem. (1994) 37:636; Maillard J. Pharm. Sci. (1994) 83:46).

The exemplary reaction schemes used to synthesize protected heterocyclic base compounds shown below utilize cHPMPC as an example.
 10 Analogous reactions will generate compounds comprising other Z moieties such as -CH₂-O-CH₂-CH₂- or -CH₂-O-CH(CH₃)-CH₂- linked to B¹. Phosphonate alkyl and aryl esters of compounds comprising B¹ are prepared, using HPMPC and cHPMPC as an example, according to the following procedures

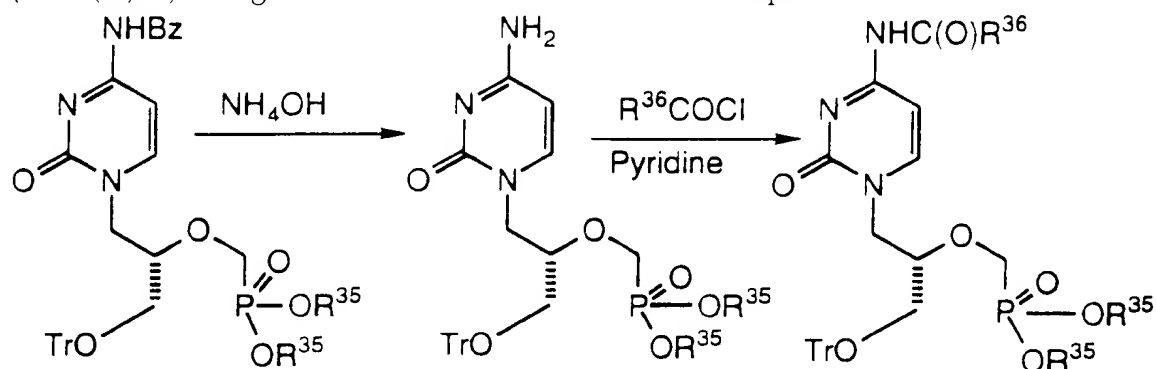


20 Exemplary R³⁵ and/or R³⁶, which can be the same or different, include

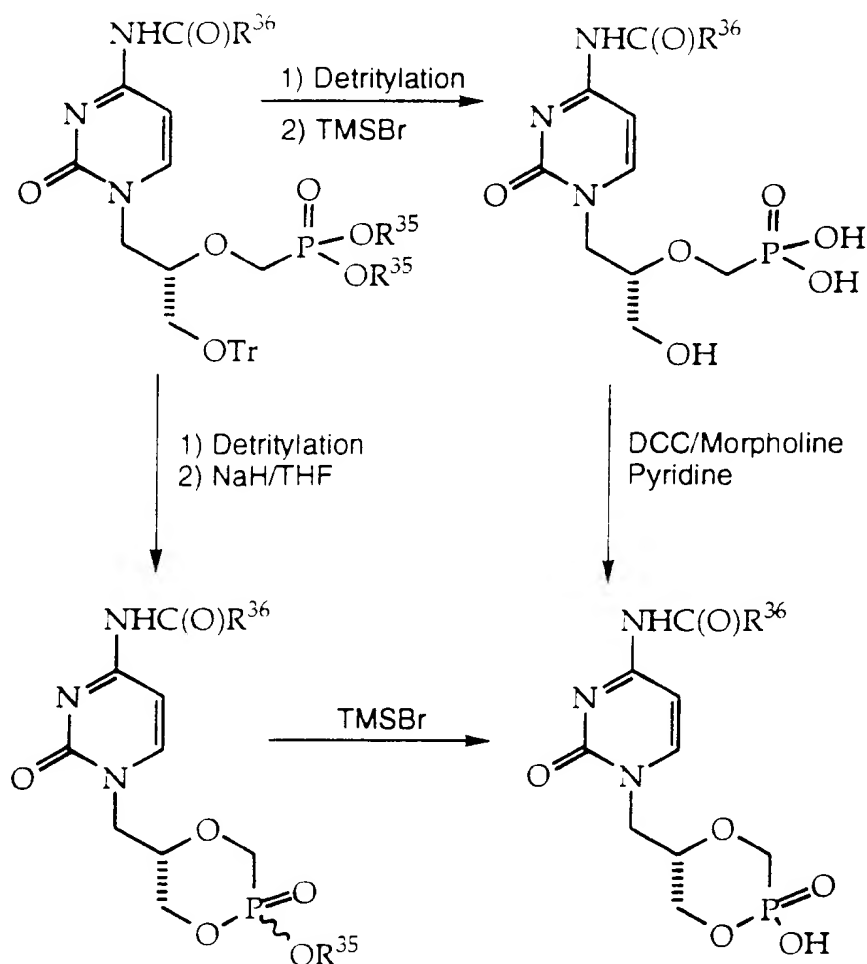
phenyl, substituted phenyl, $-C_{10}H_{15}$ (where $C_{10}H_{15}$ is adamantoyl), $-CH_2-C_6H_5$, $-C_6H_5$, $-C(CH_3)_3$, $-CH(CH_3)_2$, $-CH_2CH_3$, methyl, ethyl, butyl, t-butyl, heptyl, nonanyl, undecanyl, lauryl, steryl, undecenyl and the like. The amide linkage is conveniently formed by reaction of the acyl chloride with the exocyclic
5 amine linked to the base. When R^1 is linked to the free phosphonate the resulting ester will comprise a single isomer or a scalemic mixture at the phosphorus atom. Low temperature reaction conditions (lower than about -20° , e.g., about -20° to about -40° C or about -40° to about -80° C) tend to favor single isomer products, while reaction at higher temperatures (above
10 about -20° , e.g. -20° to 40° C) generally results in a scalemic mix. When a scalemic mixture is obtained, the isomers can be conveniently separated by, for example, HPLC, although the mixture can be used, for example, as a synthetic intermediate or as an active antimicrobial agent, without resolution. Synthesis of the phenyl ester of cHPMPC at -78° C by reaction of
15 the chloridate and phenoxide yielded a scalemic mixture consisting of about $\geq 90\%$ of the product as one isomer (isomer #1) at the phosphorus atom while the remaining $\sim \leq 10\%$ was present as the other isomer (isomer #2). The scalemic mixture was converted to isomer #2 ($\geq 90\%$) by incubation at room temperature for about 10 minutes (about 10 to 30 minutes is generally
20 suitable) with a catalytic amount of sodium phenoxide in DMF. This method can be used to convert one isomer of cHPMP-B or cHPMP-B¹ (such as cHPMPC or cHPMPA) aryloxy or alkoxy ester to the other isomer with catalytic amounts of the corresponding aryloxy ion or alkoxide ion.

The cHPMPC pivaloyloxymethyl ester synthesis yields a scalemic
25 mixture at the phosphorus atom. The mixture was separated by HPLC into the two isomers which were then exposed to an rat intestinal homogenate or to a rat intestinal wash. One of the isomers was converted to cHPMPC after incubation in the homogenate while the other isomer was converted to HPMPC pivaloyloxymethyl monoester. Both isomers were converted to
30 HPMPC pivaloyloxymethyl monoester after incubation in the intestinal wash. These results suggested that (1) in at least some cases, enzyme activity can have a differential effect on the metabolic fate of a cHPMPC ester depending on which phosphorus isomer is present and (2) chemical activity (i.e., the acidity of the intestinal wash) can affect the metabolic fate of a given
35 compound in a manner that differs from enzyme activity.

A method to obtain heterocyclic bases comprising the $C(O)R^{36}$ protecting group is accomplished as follows using the acyl chloride ($R^{36}C(O)Cl$) using HPMPC and cHPMPC as an example

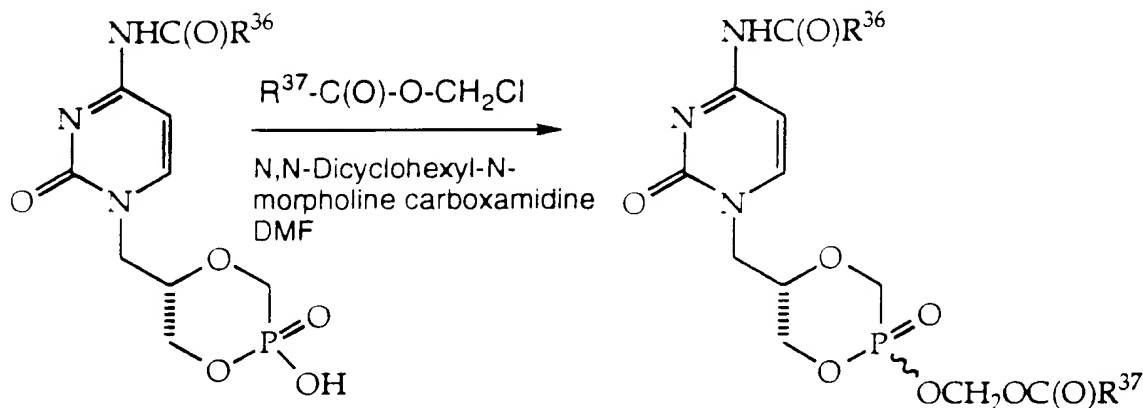


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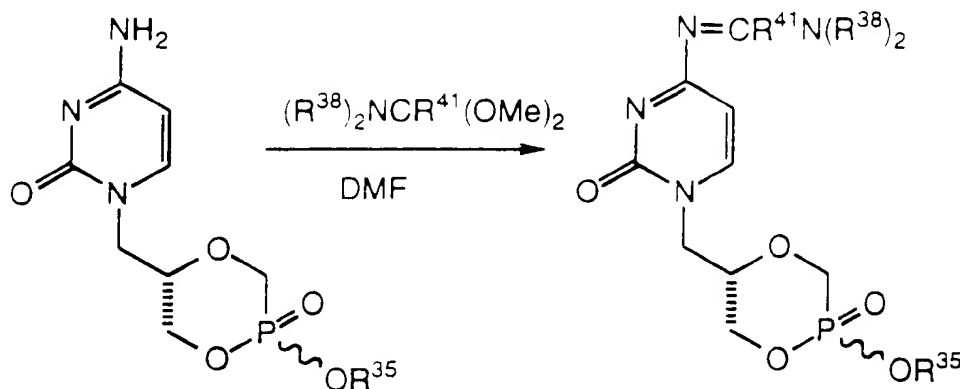
wherein Tr is the hydroxyl protecting group trityl. The detritylation step is accomplished by acid treatment, such as 80% acetic acid at about 10° to 60° C for 1-2 hours. The R³⁵ moiety is removed using a Lewis acid such as TMSBr to yield the free phosphonate.

Phosphonate compounds comprising B¹ and a C₂-C₂₀ 1-acyloxy-1-alkyl or a C₄-C₂₀ 1-acyloxy-1-alkyl-1-aryl ester group are prepared as follows



wherein R³⁷ is C₁-C₂₀ alkyl which is unsubstituted or substituted by substituents independently selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl (1 to 3 halogen atoms), cyano, nitro, OH, O, NH and halogen (including ethyl, propyl, isopropyl, t-butyl, isobutyl and adamantoyl), or C₃-C₁₀ aryl which is unsubstituted or substituted by substituents independently selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl (1 to 3 halogen atoms), cyano, nitro, OH, O, N and halogen (including phenyl, and 3- or 4-pyridyl).

The amine protecting group =CR⁴¹N(R³⁸)₂ is incorporated into an exocyclic amine to yield protected heterocyclic base compounds as follows



Exemplary R³⁸ alkyl groups include methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl and cyclobutyl. In general, both R³⁸ alkyl groups will be the same. The reaction can be carried out in dry DMF at room temperature (about 20-30° C) as previously described (Kerr et al *J. Pharm. Sci.* (1994) **83**:582; Kerr et al *J. Med. Chem.* (1992) **35**:1996), or DMF can be substituted with CH₃CN and 4 Å molecular sieves. Exemplary compounds include species where R is hydrogen, alkyl (including ethyl, propyl, isopropyl), aryl (including phenyl) or acyloxymethyl. Protected heterocyclic bases where R⁴¹ is hydrogen are stable under neutral anhydrous conditions and are generally labile under acidic aqueous conditions. When R⁴¹ is methyl, the protecting group is more stable to aqueous acidic or basic conditions.

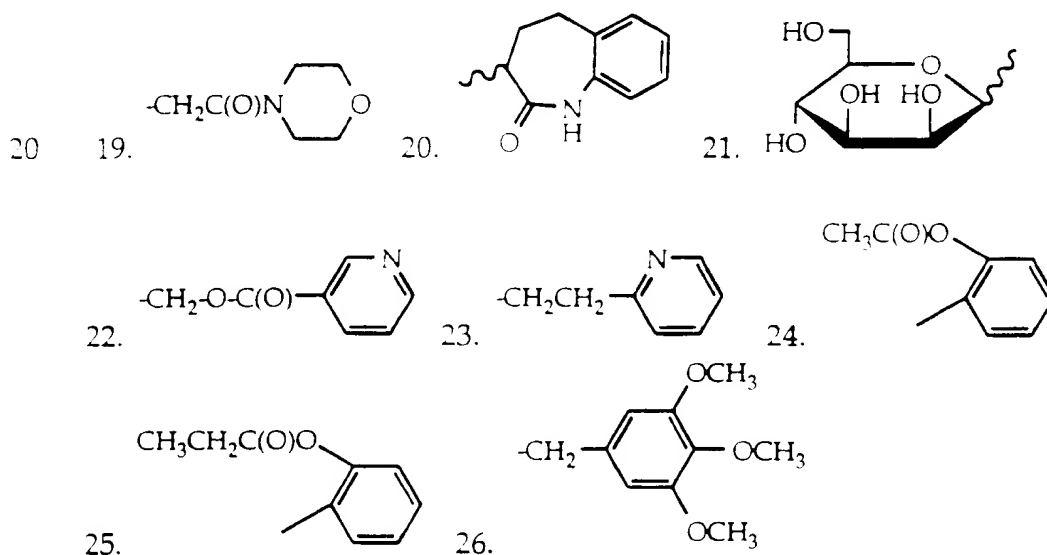
Compounds containing a protected heterocyclic base and 1 or 2 amino acids, dipeptides or oligopeptides attached to the phosphorus atom via an amidate linkage are obtained as described for synthesis of bis-amidate or amidate-ester compounds.

Table 5A lists R³⁵ ester and L¹ amidate moieties that can be incorporated into the phosphorus atom of both cyclic Z moieties (such as cHPMPC comprising a protected heterocyclic base or cHPMPC) or linear Z moieties (such as HPMPC comprising a protected heterocyclic base or PMEA comprising a protected heterocyclic base or PMEA). Esters of structures 1-5, 8-10 and 16, 17, 19-22 are synthesized by reacting a nucleotide analog (such as cHPMPC) the corresponding halide (chloride or acyl chloride and the like) and N,N-dicyclohexyl-N-morpholine carboximidine (or another base such as DBU, triethylamine, CsCO₃, N,N-dimethylaniline and the like) in DMF (or

other solvent such as acetonitrile or N-methylpyrrolidone). Esters of structures 5-7, 11, 12, 21, and 23-26 are synthesized by reaction of the alcohol or alkoxide salt (or the corresponding amines in the case of compounds such as 13, 14 and 15) with a nucleotide analog monochlorophosphonate or dichlorophosphonate (such as cHPMPC monochlorophosphonate or PMEA dichlorophosphonate) or another activated phosphonate.

TABLE 5A

- | | | |
|----|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| | 1. $-\text{CH}_2-\text{C}(\text{O})-\text{N}(\text{R}^7)_2^*$ | 10. $-\text{CH}_2-\text{O}-\text{C}(\text{O})-\text{C}(\text{CH}_3)_3$ |
| 10 | 2. $-\text{CH}_2-\text{S}(\text{O})(\text{R}^7)$ | 11. $-\text{CH}_2-\text{CCl}_3$ |
| | 3. $-\text{CH}_2-\text{S}(\text{O})_2(\text{R}^7)$ | 12. $-\text{C}_6\text{H}_5$ |
| | 4. $-\text{CH}_2-\text{O}-\text{C}(\text{O})-\text{CH}_2-\text{C}_6\text{H}_5$ | 13. $-\text{NH}-\text{CH}_2-\text{C}(\text{O})\text{O}-\text{CH}_2\text{CH}_3$ |
| | 5. 3-cholesteryl | 14. $-\text{N}(\text{CH}_3)-\text{CH}_2-\text{C}(\text{O})\text{O}-\text{CH}_2\text{CH}_3$ |
| | 6. 3-pyridyl | 15. $-\text{NHR}^{40}$ |
| 15 | 7. N-ethylmorpholino | 16. $-\text{CH}_2-\text{O}-\text{C}(\text{O})-\text{C}_{10}\text{H}_{15}$ |
| | 8. $-\text{CH}_2-\text{O}-\text{C}(\text{O})-\text{C}_6\text{H}_5$ | 17. $-\text{CH}_2-\text{O}-\text{C}(\text{O})-\text{CH}(\text{CH}_3)_2$ |
| | 9. $-\text{CH}_2-\text{O}-\text{C}(\text{O})-\text{CH}_2\text{CH}_3$ | 18. $-\text{CH}_2-\text{C}\equiv\text{H}(\text{OC}(\text{O})\text{CH}_2\text{R}^7)-\text{CH}_2-$
$(\text{OC}(\text{O})\text{CH}_2\text{R}^7)^*$ |



* - Each R^7 is the same or different (includes methyl, ethyl, propyl, isopropyl and t-butyl).

All citations are hereby expressly incorporated by reference. The following examples are illustrative and do not limit the scope of this invention.

5 Example 1: Synthesis of phosphonate amidate compounds. The compounds of structural formula Id shown are in Table 6 (bis(glycyl benzyl ester)PMEA (compound Ex 4), bis(alanyl benzyl ester)PMEA (Ex 1), bis(phenylalanyl benzyl ester)PMEA (Ex 5), etc. Compounds Ex 1 - Ex 12 were synthesized by the following procedure. PMEA (Z-B = -CH₂-O-CH₂-CH₂-B, 10 where B is adenin-9-yl) (0.3 g; 1.1 mmol) and amino acid ester•HCl (2.2 mmol; Sigma) were suspended in dry pyridine (6 mL) containing triethylamine (0.3 mL; 22.2 mmol), followed by addition to a mixture of freshly prepared triphenylphosphine (3.3 mmol) and 2,2'-dipyridyl disulfide (3.3 mmol) in pyridine (3 mL). The mixture was stirred at room temperature overnight, 15 concentrated and partitioned between methylene chloride and water. The organic solution was dried over MgSO₄, concentrated and purified by flash column chromatography on silica gel.

Ex 14 was synthesized using freshly prepared triphenylphosphine (6.0 mmol) and 2,2'-dipyridyl disulfide (6.0 mmol) in pyridine (20 mL) at room 20 temperature to which PMEA (2.0 mmol) was added. The suspension was stirred for 10 min. and ethyl sarcosine HCl (N-methylglycine HCl ethyl ester; 1.2 g, 8.0 mmol) was added. The suspension was warmed to 90°C and stirred for 24 hours. Crude product was concentrated by rotary evaporation and purified by silica flash chromatography (mobile phase 1% methanol gradient 25 to 20% methanol/80% methylene chloride).

Compound Ex 13 was synthesized in a similar manner using PMEA and phenylalanine N-ethylmorpholino ester.

TABLE 6

30	Compound	L1
	Ex 1	-NH-CH(CH ₃)-C(O)OCH ₂ C ₆ H ₅
	Ex 2	-NH-CH(CH ₂ C ₆ H ₅)-C(O)OCH ₂ C ₆ H ₅
	Ex 3	-NH-CH(CH ₂ CH(CH ₃) ₂)-C(O)OCH ₂ C ₆ H ₅
	Ex 4	-NH-CH ₂ -C(O)OCH ₂ C ₆ H ₅
35	Ex 5	-NH-CH(CH ₃)-C(O)OC ₂ H ₅

Ex 6	-NH-CH(CH ₂ CH(CH ₃) ₂)-C(O)OC ₂ H ₅
Ex 7	-NH-CH ₂ -C(O)OC ₂ H ₅
Ex 8	-NH-CH(CH ₂ C ₆ H ₅)-C(O)OC(CH ₃) ₃
5 Ex 9	-NH-CH(CH ₂ CH(CH ₃) ₂)-C(O)OC(CH ₃) ₃
Ex 10	-NH-CH(CH ₃)-C(O)OC(CH ₃) ₃
Ex 11	-NH-CH ₂ -C(O)OC(CH ₃) ₃
Ex 12	-NH-CH(CH ₂ C ₆ H ₅)-C(O)OC ₂ H ₅
Ex 13	-NH-CH(CH ₂ C ₆ H ₅)C(O)O-(CH ₂) ₂ -N[(CH ₂) ₂ (CH ₂) ₂]O
10 Ex 14	-N(CH ₃)-CH ₂ -C(O)OC ₂ H ₅

Example 2: Antiviral activity. Compounds were individually tested for activity against HSV-1 and/or HSV-2. HSV-2 (strain 414-92) was tested using MA 104 cells in the following assay protocol. 96-Well plates were seeded with 1×10^4 MA 104 cells per well using 200 μ L minimal essential medium (MEM) containing 10% calf serum per well, and incubated overnight at 37°C. The compounds were dissolved in MEM Earle's Salts without serum. The medium was removed by aspiration and 100 μ L MEM Earle's Salts without serum was added to the wells. Serial 3-fold dilutions of the compounds were prepared by serial transfer of 50 μ L of medium from wells containing compound to wells lacking compound. The plates were incubated 15 minutes at 37°C followed by addition of 100 PFU/well of virus in MEM Earle's Salts with 2% fetal bovine serum. The plates were then incubated at 37°C for three days until approximately 90% of the cells in virus infected control wells containing no compound were killed. Following incubation, medium was aspirated and the wells were washed with sterile PBS. 100 μ L 0.5% crystal violet in 20% methanol was then added to the wells for 5 minutes, aspirated and the wells were washed two or three times with distilled water. 200 μ L of 0.01 N HCl was added to the wells and the absorbance of each well at 595 nm was determined. The results, shown in Table 6, were expressed as the IC₅₀, the concentration (μ M) that inhibits cell killing mediated by HSV-2 by 50%. IC₅₀ values varied from 2 μ M to >100 μ M compared to an IC₅₀ for PMEA of 21 μ M. Thus, some of the compounds were more active against HSV-1 than

PMEA.. The toxicity of the compounds were expressed as the CC₅₀, the concentration that kills 50% of uninfected cells.

The compounds were also tested for activity against the KOS strain of HSV-1 in VERO cells. The results, shown in Table 7, were expressed as the EC₅₀, the concentration (μM) that inhibits cell killing mediated by HSV-2 by 50%. EC₅₀ values varied from 2 μM to >200 μM compared to an EC₅₀ for PMEA of 138 μM. Thus, some of the compounds were more active against HSV-2 than PMEA.

Table 7

10

compound	HSV-1	HSV-2	
	EC ₅₀	IC ₅₀	CC ₅₀
Ex 7	>200	>100	>100
Ex 5	nt*	>100	>100
Ex 6	20	33	>100
Ex 12	nt	20	80
Ex 11	>200	>100	>100
Ex 10	>200	>100	>100
Ex 9	63	63	>100
Ex 8	3	9	20
Ex 4	nt	60	>100
Ex 1	nt	20	>100
Ex 3	nt	2	30
Ex 2	nt	4	20

* nt - not tested

Example 3: PMEA, monophenyl ester, mono N-ethylmorpholino-
phenylalanyl phosphoroamidate. Bis(phenyl)PMEA is selectively hydrolyzed
 15 to the monophenyl ester of PMEA using NaOH in THF. The reaction
 mixture is neutralized with acid (1 N HCl), and the monophenyl PMEA is
 isolated by filtration. The anhydrous monophenyl PMEA and 2 equivalents
 of a freshly prepared 1:1 mixture of triphenylphosphine and 2,2'-dipyridyl
 20 disulfide in pyridine is condensed with 1 equivalent of phenylalanine N-
 ethyl-morpholino ester in triethylamine and pyridine to afford the title

compound. The title compound is recovered by evaporation of the solvents under reduced pressure and purified by silica gel chromatography.

Example 4: Antiviral activity of PMEAs esters. PMEAs and PMEAs esters were tested for inhibition of cytopathic effects by HSV II in MA 104 cells as described except that CPE was determined after incubation with virus by addition of 100 μ L XTT, 1 mg/mL in deficient DME containing 25 μ M PMF followed by measuring absorbance. The esters tested were bis(POM)PMEA, bis(phenyl)PMEA, monophenylPMEA, bis(3-dimethylaminophenyl)PMEA, bis(3-methoxyphenyl)PMEA, bis(2-carboethoxyphenyl)PMEA, bis(adamantoyloxymethyl)PMEA, bis(4-fluorophenyl)PMEA and bis(2-ethoxyphenyl)PMEA. All of the compounds tested were active, which indicated that the ester groups were removed, thereby allowing free PMEAs to inhibit virus replication and/or cytopathic effects. The IC₅₀ and CC₅₀ of PMEAs in the assay was 19.3 μ M and 2000 μ M respectively and the IC₅₀ and CC₅₀ of bis(POM)PMEA in the assay was 0.5 μ M and >10 μ M respectively. IC₅₀ values for the mono and bis esters ranged from 1.1 μ M to 67.5 μ M and the CC₅₀ values ranged from 70 μ M to 500 μ M.

Example 5: Oral bioavailability of nucleotide analog amidates and PMEAs esters. Nucleotide analog amidates and nucleotide analogs are tested for their bioavailability when administered to cynomolgous (or rhesus) monkeys by oral, subcutaneous or intramuscular routes. Bioavailability is determined by measuring PMEAs levels in plasma or urine at different times after administering the drug using radiolabeled (³H, ¹⁴C, etc) compound or, for compounds having adenine, essentially as described (Naesens, et al, Clin Chem (1992) 38:480-485; Russell, et al, J Chromatogr (Netherlands) (1991) 572:321-326). Radiolabeled compounds are obtained commercially (Moravsek Biochemicals, Brea, CA) or by standard procedures, such as catalytic hydrogen exchange for ³H labeling. Compounds such as bis(2-ethoxyphenyl)PMEA, bis(2-carboethoxyphenyl)PMEA, bis(O-benzylphenylalanyl)PMEA, bis(3,5-dimethoxyphenyl)PMEA, bis(4-fluorophenyl)PMEA, bis(adamantoyloxymethyl)PMEA, bis(phenyl)PMEA, bis(3-methoxyphenyl)PMEA are tested for oral bioavailability by administering about 10 - 30 mg/Kg (usually 15 to 25 mg/Kg) containing about 20 - 50 μ Ci/Kg (usually about 40 μ Ci/Kg) of

radiolabeled compound, followed by withdrawing blood samples at several times after administration (exemplary time points are 0.1, 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4, 6, 12, 18, 24, 36, 48, 72, 96 hours after administration), obtaining plasma and determining the amount of radiolabeled compound present per volume (about 0.1 - 1.0 mL) of serum. Oral bioavailability of the tested compounds is 2 - 80% (or any value between 2% and 80% in 1% increments), preferably 10 - 80% and more preferably 15 to 80%. The oral bioavailability of bis(POM)PMEA by this type of assay is typically about 25% in monkeys and PMEA is about 2 - 4% (Balzarini et al, Animal Models in AIDS (1990) p. 131-138, Schellekens, H. et al (ed), Elsevier Science Publications, Amsterdam) while nucleotide analog amidates and nucleotide analogs (including mono- and diesters) can have oral bioavailabilities of about 5%, 10%, 15%, 30%, 40%, 50%, 60% or 80%.

Total radioactivity in plasma is determined by mixing about 200 μ L of plasma with a scintillation counting cocktail (such as 10 mL of Scinti-Safe plus LSC cocktail) and counting in a scintillation counter (usually for about 5 - 30 minutes). Detailed analysis of the radiochemical composition is accomplished using about 350 μ L of plasma, denaturing proteins in the serum (using about 700 μ L 0.1% trifluoroacetic acid in acetonitrile for example), drying the resulting sample under reduced pressure, suspending the sample in an appropriate buffer (for example using about 100 μ L of 2% acetonitrile in 25 mM potassium phosphate buffer with 10 mM tetrabutyl ammonium hydrogen phosphate (TBAHP), pH 6.0 for HPLC analysis), centrifuging the sample and analyzing the supernatant for individual radiolabeled species by reverse phase HPLC on commercially available columns (The Separation Group, Hesperia, CA; Vydac C18, 5 μ m, 250 x 4.6 mm column with an injection volume of about 50 μ L and a flow rate of about 1.0 mL/min. at about 35°C using buffer for 2 minutes followed by a linear gradient to about 65% acetonitrile in 25 mM potassium phosphate buffer with 10 mM TBAHP, pH 6.0 over 13 about minutes). Radiolabel detection is accomplished using means such as commercially available radioactive flow detection systems or scintillation counting systems (Packard, Meridian, CT).

Fluorescence detection of PMEA in plasma is accomplished by measuring fluorescence emission (420 nm, with excitation at about 236 nm) with a detector (model F2000, Spectra Physics, San Jose, CA) from the HPLC

gradient essentially as described above (2 to 65% acetonitrile). Samples for analysis are prepared from plasma (200 μ L) by protein precipitation with TFA (400 μ L 0.1% in acetonitrile), drying and conversion of adenine to N6-ethenoadenine in 200 μ L of reaction buffer (0.34% chloroacetaldehyde, 100 mM sodium acetate, pH 4.5) for 40 minutes at 95°C followed by HPLC analysis using 50 μ L.

Example 6: Bis(adamantoyl oxymethyl)PMEA ester. DBU (1,8-diazabicyclo[5.4.0]undec-7-ene; 1.53 g, 10 mmol) was added to a suspension of PMEA (1.365 g, 5 mmol) in DMF (25 mL). Adamantoyl oxymethyl chloride (5.72 g, 25 mmol) in DMF (25 mL) was added to the reaction mixture which was then stirred for four days at room temperature and the volatiles were removed under vacuum. The crude product obtained after removal of the solvent was loaded onto a silica gel column and washed with 3% MeOH/ CH_2Cl_2 to remove nonpolar impurities. 1 g (30%) of bis(adamantoyl oxymethyl)PMEA ester was eluted in 8% MeOH/ CH_2Cl_2 . Adamantoyl oxymethyl chloride was obtained by conversion of 1-adamantanecarbonyl chloride (Aldrich No. 11,772-2) with $(\text{CH}_2\text{O})_n/\text{ZnCl}_2$ and has been described (Bodor, et al J Med Chem (1980) **23** :474-480).

Example 7: Bis(phenyl)PMEA and bis(2-ethoxyphenyl)PMEA esters. PMEA (2.0 g, 7.3 mmol), acetonitrile (20 mL), thionyl chloride (20 mL) and N,N-dimethylformamide (2 drops) were added to a 250 mL single neck round bottom flask equipped with a magnetic stirrer, water cooled condenser and N_2 atmosphere. The flask was immersed in a 85°C oil bath and the resulting suspension was stirred for two hours. The resulting solution was then concentrated to dryness and acetonitrile (50 mL) was added to redissolve the crude chloridate.

To a separate 250 mL single neck round bottom flask equipped with a mechanical stirrer, and N_2 atmosphere, phenol (3.25 g, 35 mmol), tetrahydrofuran (80 mL) and sodium hydride (1.4 g, 34 mmol, 60% (w/w) dispersion in mineral oil) was charged. After stirring for 30 minutes, the solution was cooled to -78°C with a dry ice-acetone bath. The acetonitrile from the previous step was then added drop-wise at a rate that the internal temperature did not rise above -76°C. After the addition was complete, the

resulting suspension was poured into saturated aqueous NaHCO_3 (100 mL) and extracted with methylene chloride (3 x 150 mL). The combined organic extracts were washed with H_2O (100 mL), brine (100 mL) and dried with anhydrous Na_2SO_4 . Concentration by rotary evaporation afforded a yellow solid. Purification by recrystallization (ethyl acetate/hexanes) afforded pure bis(phenyl)PMEA (1.64 g, 53%). Bis(2-ethoxyphenyl)PMEA was made similarly using 2-ethoxyphenol in place of phenol in 36% yield.

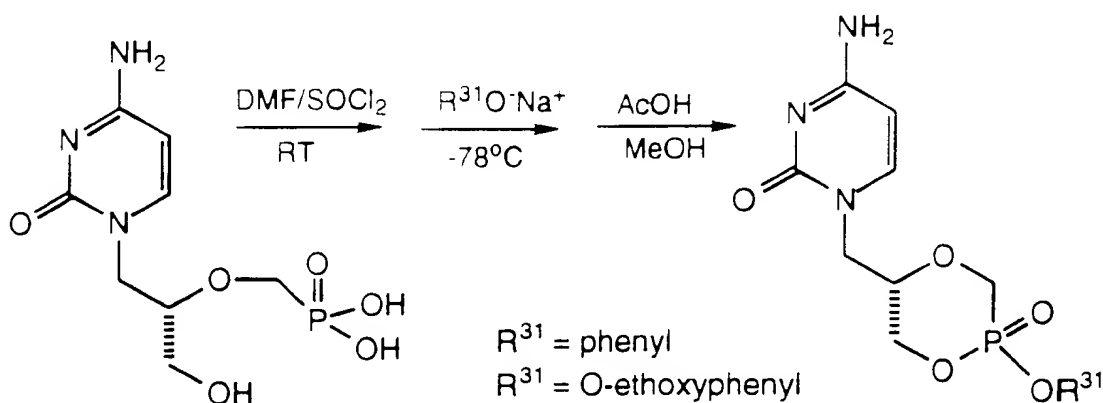
Example 8: (R)-9-(2-Di-2 ethoxyphenylphosphonylmethoxypropyl) adenine. To a solution of 2-ethoxyphenol (45 mmol, 6.22 g) in pyridine (75 mL) was added (R)-9-(2-phosphonylmethoxypropyl adenine (PMPA, 15 mmol, 4.3 g), creating a white suspension. A separate solution of 2,2'-dipyridyl disulfide (45 mmol, 9.91 g) and triphenyl phosphine (45 mmol, 11.81 g) in pyridine (75 mL) was added at 22°C in a single portion to the white suspension. Then, triethylamine (30 mmol, 4.18 mL) was added in a single portion to the entire mixture, which was stirred at 75°C for 21 h (TLC:10% MeOH/EtoAc). The dark amber slurry was then coevaporated with toluene (100 mL). It was then dissolved in dichloromethane (200 mL) and extracted twice with water (200 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated (*in vacuo*) to a brown syrup (25.4 g). The syrup was purified by flash chromatography: 1-5% MeOH/EtoAc to elute impurities, then 6-12% MeOH/EtoAc (title compound elutes at 10-11%). The desired fractions were concentrated to afford 1.04 g of a brown solid. The solid was then recrystallized (EtoAc) to give the title compound (780 mg, 12% yield) as a tan solid. ^1H NMR (CDCl_3) δ 1.25 (d, $J=7.5\text{Hz}$, 3H, CH_3), δ 1.46 (m, 6H (OCH_2CH_3)₂), 4H (OCH_2CH_3)₂, δ 3.9 (m, 2H, O- CH_2P), δ 4.04 (m, 1H, H-2'), δ 4.09-4.39 (m, 2H, H-1'), 7.24 (m, 8H, (C_6H_4)₂), 7.92 (s, 1H, ($\text{C}_8\text{-H}$)), 8.19 (s, 1H, $\text{C}_2\text{-H}$).

Example 9: cHPMPU. cHPMPU was synthesized by adding thionyl chloride (60 mL, 0.812 mmol, 2.02 eq) dropwise to a suspension of disodium HPMPU (131 mg, 0.404 mmol) in *N,N*-dimethylformamide (1.25 mL) at ambient temperature. The resulting light-yellow solution was stirred for 20 min at ambient temperature and then concentrated to dryness (*in vacuo*, 45 °C). H_2O (2 mL) was added and the resulting solution was concentrated to dryness. Methanol (4 mL) was added and the resulting solution was

concentrated to dryness to afford the crude product as a light-yellow solid. Purification by silica flash chromatography (mobile phase: 30% methanol: 70% CH₂Cl₂ gradient to 50% methanol: 50% CH₂Cl₂) afforded pure cHPMPU in 69% yield as a white amorphous solid. ¹H NMR (300 MHz, D₂O) δ 7.62 d (1H, *J* = 7.1 Hz, CH=CH), 5.82 d (1H, *J* = 7.8 Hz, CH=CH), 4.30-3.71 m (7H, CH₂CH(OCH₂P)CH₂OH), NH and OH not observed in D₂O. ¹³C NMR (75 MHz, D₂O) δ 169.6 s (4-C), 155.1 s (2-C), 150.4 s (6-C), 104.2 s (5-C), 76.71 d (*J*_{P,C} = 3.6 Hz, 2'-CH₂), 72.30 d (*J*_{P,C} = 6.2 Hz, 3'-CH₂), 67.90 d (*J*_{P,C} = 142.0 Hz, P-CH₂), 50.71 s (1'-C). ³¹P NMR (121 MHz, D₂O) δ 9.23 s.

Example 10: cHPMPC ethyl ester. To a stirred solution of diethyl HPMPC (1.1g) in DMF, NaH (115 mg) was added. After 15 min, the reaction mixture was quenched with acetic acid (1 eq). The solvents were removed under reduced pressure. The crude mixture was dissolved in CH₂Cl₂ and water. The organic layer was washed with NaCl solution and the crude material obtained was purified on a silica gel column (elution with 5%-10% MeOH in CH₂Cl₂) to get cyclic ethyl HPMPC (950 mg) as a diastereomeric mixture (approximately 70%).

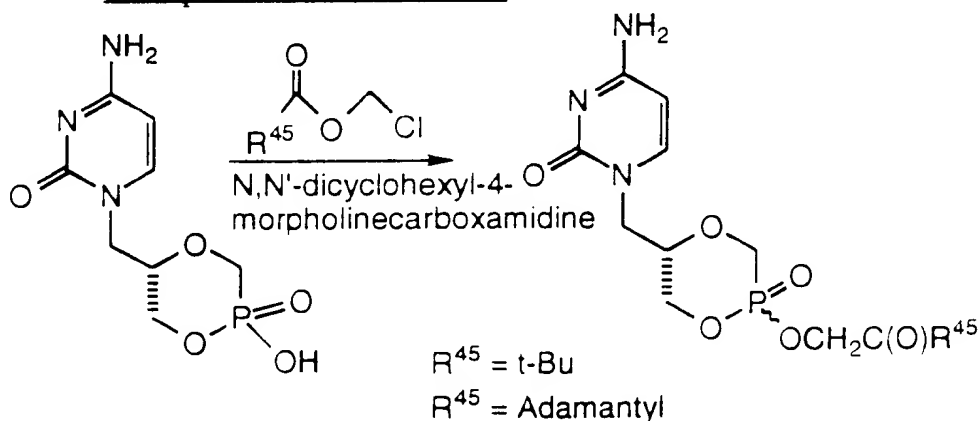
Example 11: cHPMPC esters.



To a stirred suspension of HPMPC (2.79 g) in DMF, thionylchloride (2.1 mL) was added dropwise under anhydrous conditions and the mixture was stirred for 1 hr. In another flask, sodium aryloxide (using the appropriate aryl substituent) was made using the corresponding phenol (8.9 g) and NaH (1.8 g)

in 1:1 DMF/THF (50 mL). This solution was cooled to -78°C and the chloridate solution was added dropwise under anhydrous conditions. After 2 hrs, the reaction mixture was quenched with acetic acid (5 eq) and the solvents were evaporated under vacuum. The crude mixture was partitioned between water and CH₂Cl₂. The organic layer was concentrated and the residue was purified on a silica gel column (elution with 5%-10% MeOH in CH₂Cl₂) to get the cyclic aryl compound as a single diastereomer in approximately 60% yield. This method is suitable for all substituted or unsubstituted R³¹ groups, especially aryl, subject of course to conventional protection of labile groups other than amino for which reaction is undesired (amino is protected by reaction with DMF and deprotected with acetic acid and alkanol treatment). This method offers the advantages of producing substantially stereochemically pure product, superior yield and ease of synthesis.

Example 12: cHPMPC esters.



To a stirred suspension of cyclic HPMPC (1 mmol) was added N,N'-dicyclohexyl-4-morpholinecarboxamidine (2 mmol) followed by the corresponding acyloxymethyl chloride (1.5 mmol). The reaction was stirred for 3 days and the DMF was evaporated under reduced pressure. The crude was purified on a silica gel column (eluted with 5% methanol in methylene chloride) to get the pure cyclic HPMPC derivatives (approximately 30% yield).

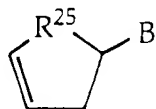
The final product was obtained in higher yield by the same reaction using cyclic HPMPC (1 mmol), N,N'-dicyclohexyl-4-morpholinecarboxamidine (1.1 mmol) followed by the corresponding acyloxymethyl chloride (1.2 mmol). N⁴-benzoyl cHPMPC pivaloyloxymethyl ester was

synthesized in a similar manner using N⁴-benzoyl cHPMPC as the starting material.

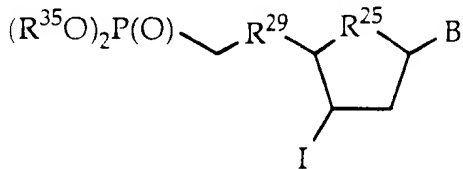
Example 13: cHPMPC esters.

cHPMPC esters were synthesized using appropriate reactants essentially as described in Example 11 for ester moieties corresponding to structure numbers 6, 7, 11, 12, 13, 23, 24, 25 and 26 in Table 5A. cHPMPC esters were synthesized using appropriate reactants essentially as described in Example 12 for ester moieties corresponding to structure numbers 8, 9, 10, 16 and 17 in Table 5A. Melting point data for cHPMPC esters of compound numbers 6, 8, 9, 11, 24, 25 and 26 was as follows: cHPMPC 3-pyridyl ester (#6) - 268-273° C (decomposes); cHPMPC N-ethylmorpholino ester (#7) - 241° C; cHPMPC -CH₂-O-C(O)-C₆H₅ ester (#8) - 198-201° C; cHPMPC #9 ortho ester - 176° C; cHPMPC #11 ester - 100-250° C (decomposes); cHPMPC phenyl ester (#12) - 190° C; cHPMPC #24 ester - 218-225° C (waxy liquid); cHPMPC #25 ester - 171° C; cHPMPC #26 ester - 181° C.

Example 14: 9-[2,3-dideoxy-2,3-didehydro-4-phosphonomethoxy-β-D-erythrofuranosyl]adenine esters. Compounds where Z is of structure V and R²⁵ and R²⁹ is oxygen were synthesized by addition-elimination reaction using



, where B was adenine with iodine (2 equivalents) in acetonitrile and a compound having the structure (R³⁵O)₂P(O)-CH₂-OH (where R³⁵ was isopropyl, phenyl or 2-ethoxyphenyl) to yield the 3-



iodophosphonate diester, which was then eliminated to yield the corresponding structure V compound by reaction with 5 equivalents of sodium methoxide or DBU in anhydrous organic solvent such as methanol or tetrahydrofuran at room temperature for 12 hours.

Corresponding compounds where R²⁹ is sulfur, are synthesized by the same method using (R³⁵O)₂P(O)-CH₂-SH as a reactant. The compound of

structure $(R^{35}O)_2P(O)-CH_2-OH$ where R^{35} is isopropyl has been described (Kluge Organic Synthesis (1986) 64:80-83).

Compounds of structure $(R^{35}O)_2P(O)-CH_2-OH$ where R^{35} was phenyl or 2-ethoxyphenyl were obtained by reaction of 1 equivalent of PCl_3 with 1
5 equivalent of t-butanol at $55^\circ C$ to obtain $(R^{35}O)_2P(O)H$ (U.S. Patent 3,329,742). $(R^{35}O)_2P(O)H$ was then silylated using 1 equivalent of bis(trimethylsilyl)-trifluoroacetamide and the resulting $(R^{35}O)_2P(OTMS)$ was dried under vacuum. $(R^{35}O)_2P(OTMS)$ was then converted to $(R^{35}O)_2P(O)-CH_2-OH$ by
10 reaction in paraformaldehyde containing catalytic amounts of titanium isopropoxide (or another lewis acid such as titanium tetrachloride and the like can be used) for 12 hrs (12-16 hours) at $70^\circ C$ (65 to $75^\circ C$). The 2-ethoxyphenyl product was isolated by crystallization. The bis-phenyl product was isolated by silica gel chromatography.

bis(2-ethoxyphenyl) D4AMPI ester: 1H -NMR (300 MHz, $CDCl_3$) δ 8.38
15 (s, 1H), 7.97 (s, 1H), 7.21-6.82 (m, 9H), 6.40 (d, 1H, $J=5.7$ Hz), 6.30 (d, 1H, $J=5.8$ Hz), 6.16 (s, 1H), 5.61 (s, 2H), 4.48 (dd, 1H, $J=14$, 8.8 Hz), 4.38 (dd, 1H, $J=14$, 6.5 Hz), 4.10-3.93 (m, 4H), 1.38 (t, 3H, $J=7.1$ Hz), 1.35 (t, 3H, $J=7.1$ Hz); ^{31}P -NMR (121 MHz, $CDCl_3$) δ 14.6.

bis(phenyl) D4AMPI ester: 1H -NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H),
20 7.93 (s, 1H), 7.34 - 7.10 (m, 10H), 7.03 (s, 1H), 6.42 (d, 1H, $J=5.6$ Hz), 6.34 (d, 1H, $J=5.6$ Hz), 5.98 (s, 1H), 5.83 (s, 2H), 4.32 (dd, 1H, $J=14$, 6.5 Hz), 4.19 (dd, 1H, $J=14$, 6.5 Hz); ^{31}P -NMR (121 MHz, $CDCl_3$) δ 13.3.

$(C_6H_4(OC_2H_5)-O)_2P(O)-CH_2-OH$: 1H -NMR (300 MHz, $CDCl_3$) δ 7.36-
25 7.16 (m, 10H), 4.19 (dd, 2H, $J=6.7$, 5.9 Hz), OH not detected; ^{31}P -NMR (121 MHz, $CDCl_3$) δ 17.0.

$(C_6H_5-O)_2P(O)-CH_2-OH$: 1H -NMR (300 MHz, $CDCl_3$) δ 7.25-6.89 (m,
8H), 4.24 (d, 2H, $J=5.01$ Hz), 4.18-4.08 (m, 4H), 1.46 (t, 6H, $J=7.0$ Hz); ^{31}P -NMR (121 MHz, $CDCl_3$) δ 19.9.

30 Example 14: N⁴-benzoyl cHPMPC. The title compound was synthesized using N⁴-benzoyl HPMPC diethyl ester tritylated at the hydroxyl group as a starting material. The starting material was detritylated using acetic acid and then converted to N⁴-benzoyl HPMPC using TMSBr. The resulting
35 compound was converted to N⁴-benzoyl cHPMPC using DCC and morpholine in pyridine. The title compound was tested for activity against

HCMV in tissue culture (NHDF cell line) and was found to be active with an IC_{50} of 22 μM compared with 0.4 μM for HPMPC.

1H NMR (300 MHz, $CDCl_3$) δ 8.02 (H_6 , 1H, d, 7.2 Hz), 7.97 (aromatic, 2H, d, 7.2 Hz), 7.62 (aromatic, 1H, t, 7.2 Hz), 7.5 (aromatic, 2H, t, 7.2 Hz), 7.26 (5 H_5 , 1H, d, 7.2 Hz), 4.28 (1H, t, 14.7 Hz), 4.15 (1H, t, 10.8 Hz), 4.0 (m, 3H), 3.84(1H,m), 2.49 (1H, d, 14.1 Hz); ^{31}P -NMR (121 MHz, $CDCl_3$) δ 10.07. Melting point 243-246° C.

10 The claims shall be construed to exclude any subject matter that, at the date of the invention, would not have been patentable under applicable statutory and judicial authority.